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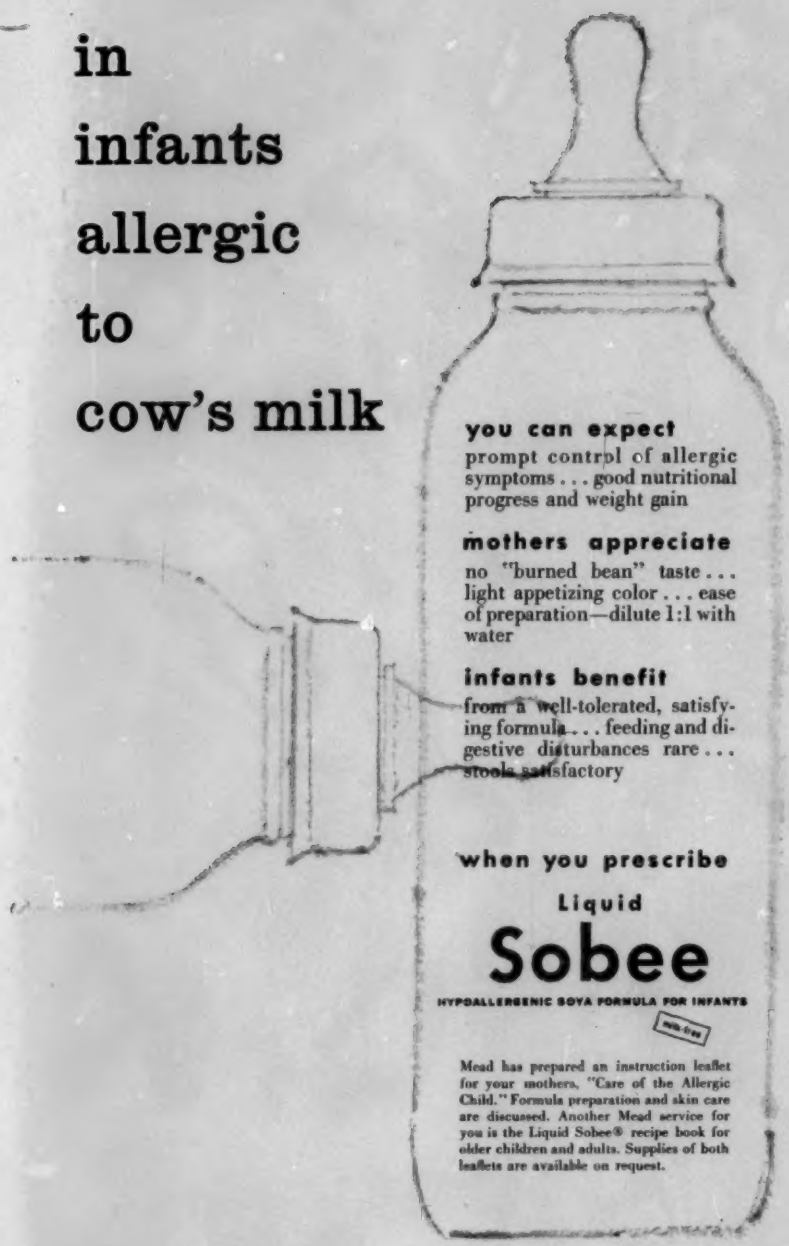

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American Journal of Diseases of Children

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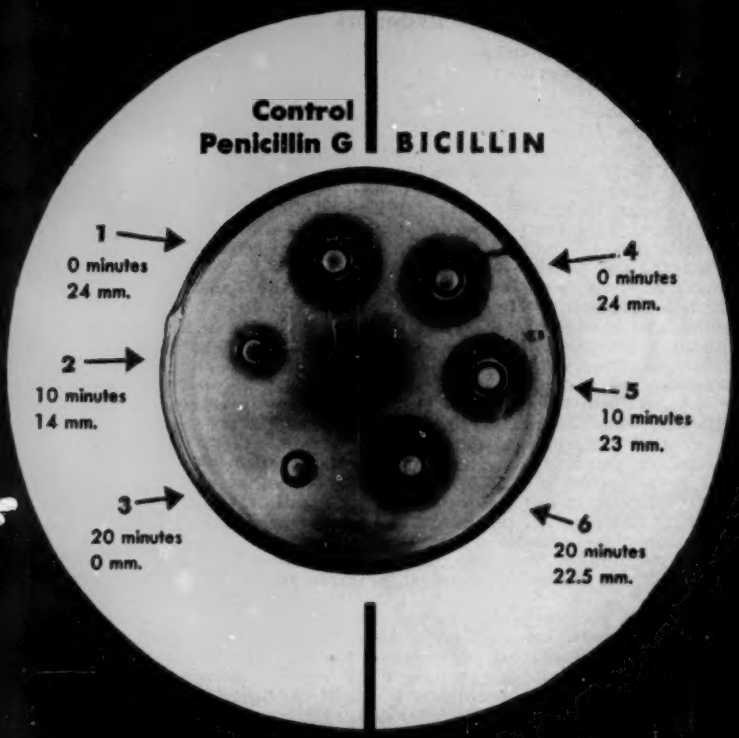

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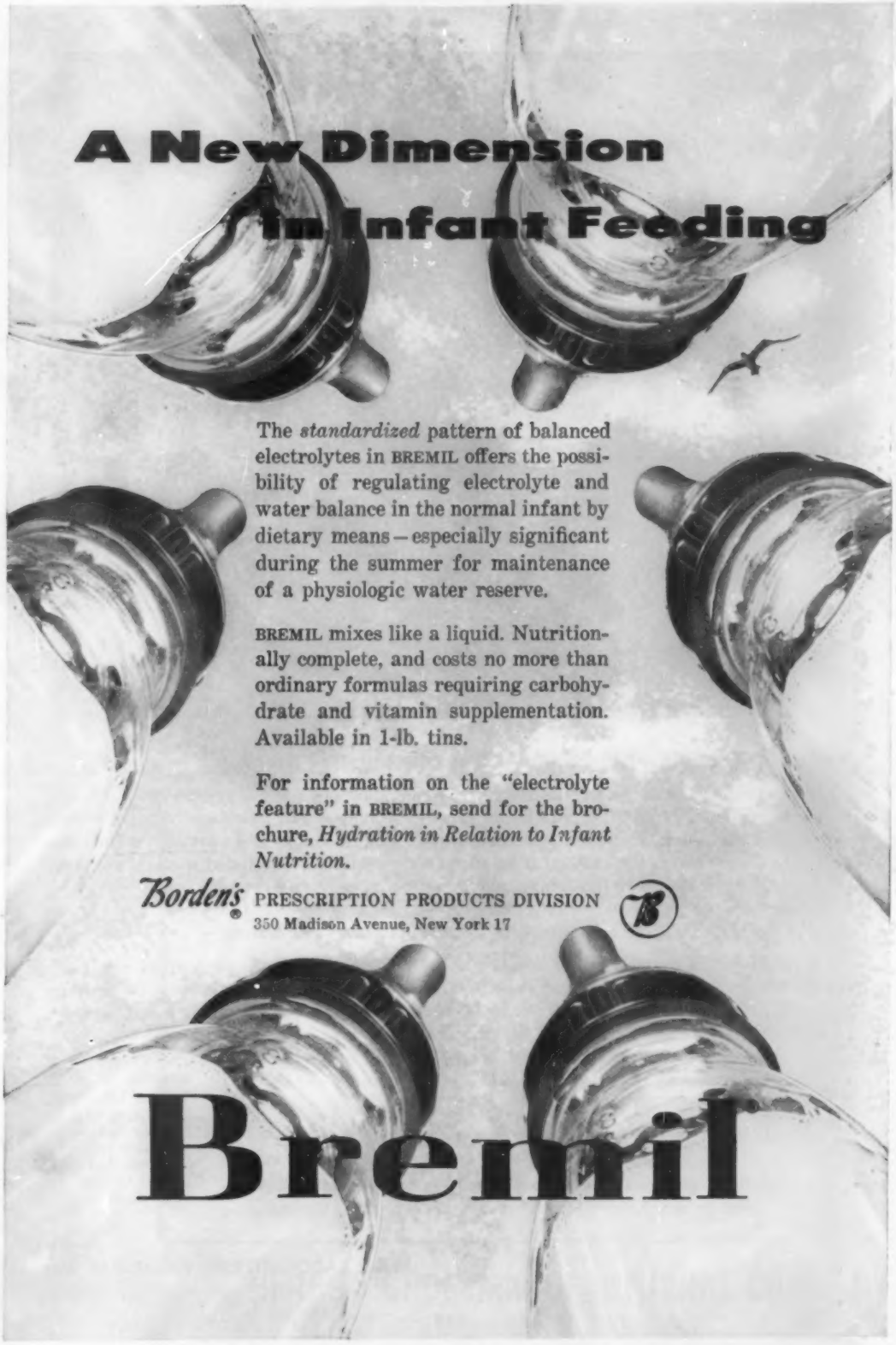
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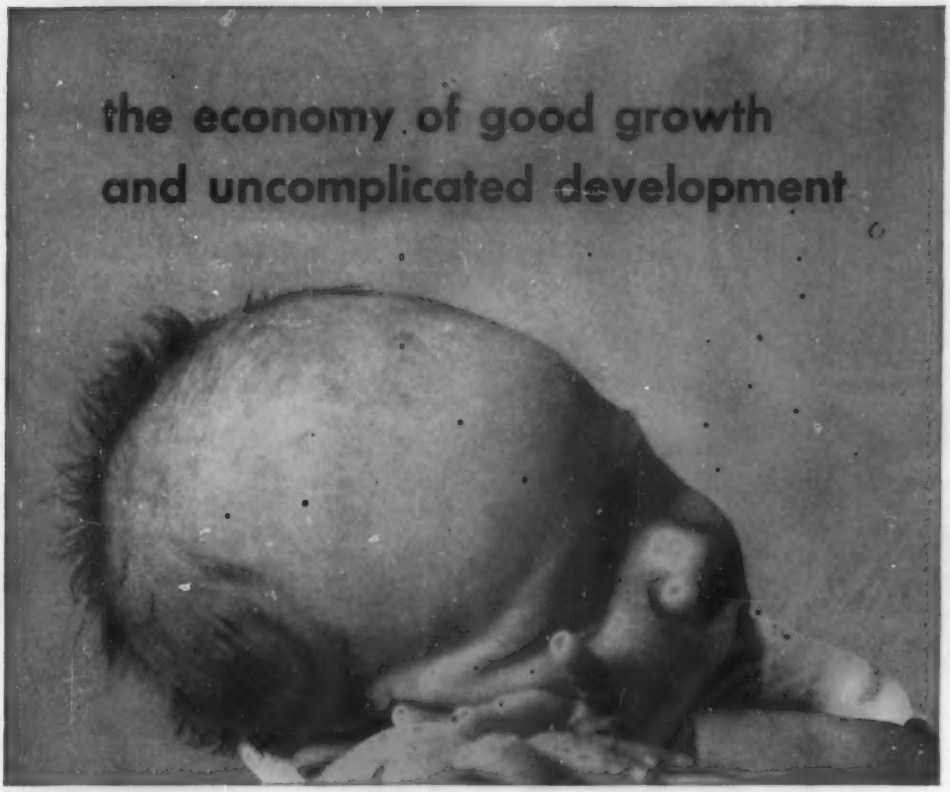

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Editorials

ADDITIONS TO THE EDITORIAL BOARD

THE EDITORIAL Board of the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN announces with pleasure the addition of three new members, Robert A. Aldrich, Richard L. Day, and Warren E. Wheeler. Dr. Aldrich takes the place of Dr. Samuel Z. Levine, a long-time and valuable member of the Board of Editors; Dr. Day fills the vacancy created when Dr. Lawson succeeded Dr. Grulee as Chief Editor, and Dr. Wheeler is filling a new position created in order to enlarge the background of the Board of Editors.

All three new editors are well known in educational and scientific circles and will bring a wealth of experience to this board. Dr. Aldrich is a native of Evanston, Ill., and graduated from Northwestern University Medical School. After an internship in the Evanston Hospital he finished his pediatric training at the University of Minnesota. Dr. Aldrich is now Associate Professor of Pediatrics at University of Oregon Medical School. He is president of the Western Society for Pediatric Research and is also a member of the American Medical Association, the Society for Pediatric Research, The American Pediatric Society, and the American Academy of Pediatrics.

Dr. Richard L. Day is a native of New York City and graduated from Harvard College and Harvard Medical School. After an internship at Hartford Hospital he finished his training at Babies Hospital and Willard Parker Hospital, in New York City. Dr. Day has recently left his position as Associate Professor at the College of Physicians and Surgeons, Columbia College Medical Department, to become Professor of Pediatrics at the State University of New York College of Medicine at New York City, Brooklyn. He is a member of the American Medical Association, The American Pediatric Society, the Society for Pediatric Research, the American Society of Human Genetics, and the American Academy of Pediatrics.

Dr. Warren E. Wheeler is a native of Youngstown, Ohio, and graduated from Mount Union College and Harvard Medical School. After interning in Pediatrics at the Massachusetts General Hospital he finished his pediatric training at the Boston Children's Hospital. Dr. Wheeler is now Professor of Pediatrics and Bacteriology at Ohio State University College of Medicine. He is a member of the American Medical Association, the American Public Health Association, the American Academy of Pediatrics, the American Society of Bacteriologists, the Society for Pediatric Research, and the American Pediatric Society.

It is a pleasure to welcome these new members to the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN, and we know they will contribute to its future growth.

Human Growth, Development, and Adaptation

Address of the American Pediatric Society President

ALFRED H. WASHBURN, M.D., Denver

The purpose of this paper is to clarify the relationship between that well-established branch of medicine called Pediatrics and the less well-defined discipline of Growth and Development. I shall not take the time to review the long and honorable history of the study of growth in all its many ramifications. As physicians our concern is with biological growth as it relates to the development of a person—a particular individual human being. Since human growth involves an especially long and significant period of maturation, my title includes the word development. Moreover, the growth of any one human organism never occurs in a vacuum but always within its own milieu, to which the growing developing organism has to adapt. Hence the title quite properly includes the word adaptation. I shall suggest that Pediatrics as a field of knowledge is essentially a subdivision of the science of Human Growth.

Many of you in this audience realize why I am deeply concerned about this problem. Part of my concern is the result of many years of effort to improve the teaching of medical students. But this is not the whole story. During the last 25 years of work with the Child Research Council I have been increasingly impressed with the tremendous challenge presented to the pediatrician in our world of today. In handling the problems of growing developing human beings he is presented with opportunities and responsibilities of tremendous significance. He has the opportunity of influencing for better or for worse the strength and character of our future citizens. He has the responsibility of safeguarding the integrity of individual human beings in a world in which the importance of a person is so often forgotten. He watches over that part of the life of a human being when he is in the process of developing into the kind of an adult he is to become. Although this seems obvious, and even trite, yet many have asked me in recent years how to teach the subject of growth and development to students, interns, or residents. If my thesis is correct, then the teaching of Pediatrics consists in the teaching of the subject of human growth, development, and adaptation.

Growth is a much misused term, which people have applied to the description of all sorts of increases in size from that of a balloon being inflated with gas to that of a child "growing up." Even when we limit ourselves to growth as a biological phenomenon it is still a difficult term to define concisely and meaningfully. In recent years the "Society for the Study of Development and Growth" has held a series of annual symposia on growth, attended by outstanding biologists, geneticists, biochemists, biophysicists, and medical scientists. The reports * of these symposia are full of food for thought for the pediatrician, even if it be true, as Keith Porter said at the 1952 meeting, that articles in the

Submitted for publication May 1, 1955.

From the Child Research Council and the University of Colorado School of Medicine.

Delivered at the Joint Meeting of The Canadian Paediatric Society, The British Paediatric Association, The Society for Pediatric Research, and The American Pediatric Society, Quebec, Canada, June 15, 1955.

* For example: The Chemistry and Physiology of Growth, Princeton, N. J., Princeton University Press, 1949 (see particularly the chapter by Paul Weiss, pp. 135-186), and The Dynamics of Growth Processes, Princeton, N. J., Princeton University Press, 1954.

literature "were alike in concluding that the phenomena of growth and differentiation are complex and very slightly understood." For my purpose today I wish merely to suggest very briefly some of the things we do know about the growth of complex multicelled organisms like Man.

We know that such growth involves the continuous process of cell multiplication—the fascinating process by which the cell creates new cells in its own image. We know that it involves the differentiation of cells to perform the many different functions of the organism so that its many millions of cells of many types may live as a biologic unit—a person with unique characteristics—one John Smith and another Mary Jones. Through the work of many brilliant scientists we know that each cell has need for specific nutrients if it is to reproduce more cells in its own image. We are able to understand, too, that as cells differentiate to perform special functions their specific needs are all-important to the healthy development of the fully grown organisms. Such needs involve not only changing requirements for specific nutrients but also adequacy of inner environment. Thus, for example, protein ceases to be just something we found hard to understand in studying biochemistry or something we arbitrarily include in set proportions in the baby's formula. The protein molecule is seen as an essential and exciting part of this process of biological growth and inner environment which we as pediatricians have professed skill in safeguarding. Or again, the mitochondria are no longer visualized as just some little dots which we were supposed to identify in histology. They have become the site of active enzyme activity so necessary to the integrity of the organism. And so one might go on for hours—but let us return to my title.

It is perfectly apparent that human growth involves much more than the mere increase in size which we record when we measure a child's height and weight from year to year. It includes the dynamic process of differentiation and development at the cellular level and of maturation of the organism, while cells function more and more effectively as organs and systems which serve the person as a whole. Some of these must be pretty well developed at birth, else the baby will not survive. Others, like the gonads or the whole brain and nervous system, may be maturing for years, each system following its own pattern.

From many brilliant experiments, with many forms of life from the single-celled neurospora to multicelled mammals, it is apparent that growth may be influenced greatly by environmental factors. From the practical standpoint of the physician it is absurd—as well as "bad medicine"—to judge a child's growth without consideration of the milieu within which it is occurring. In fact no sensible evaluation can be made of the adequacy of the child's adaptive mechanism unless one knows to what he has had to adapt. The pediatrician accepts this concept every day when he checks the baby's food intake and measures the gains in height and weight. More dramatically, he acknowledges it when he concerns himself with the effect of illnesses on the growth of different children. Some show quite amazing powers of adaptation, so that growth appears to suffer but little, even with major illnesses. Others appear to adapt with difficulty to relatively minor environmental insults, so that their growth is easily retarded or distorted.

Thus it seems logical to assume that if one professes special wisdom and skill in safeguarding the healthy growth of any individual child one must have some understanding of individual variations in the adequacy of adaptation to potentially disturbing environmental factors. Such understanding is based upon an awareness of the nature of the processes of growth and development. To summarize, then, the title suggests that human growth involves a complex but fascinating process of cell reproduction and differentiation; that it includes the development from two germ cells to a smoothly functioning multimillion-celled organism together with the continuous process of adaptation—of cells to their "milieu interieur" and of the whole organism to its external environment. Now let us turn to the word "Pediatrics."

In its most literal or narrow meaning Pediatrics is that medical science which deals with the "cure" or treatment of sick children. As a professional man the practitioner of Pediatrics professes special knowledge, skills, and understanding to be put to the service of helping sick children and their parents. No doubt most of you will say this is too narrow a definition. I shall go on to a broader concept of Pediatrics in a moment, but first let us examine the relationship of the problem of treating sick children to the concept of growth as I have tried to define it. Treating sick children is a fundamental part of pediatric practice, however defined. This suggests the need for raising two rather trite but nonetheless essential questions.

The first question is, what do we mean by a "sick" or "diseased" child. I believe it is clear that we refer ordinarily to a child who has failed to adapt to his particular environment in a manner to allow the continued orderly functioning of some one or all of his parts or systems. This may represent such an immediate acute breakdown in his adaptive powers as is seen in some overwhelming acute infections. It may involve a slow losing fight to adapt to long-continued malnutrition or a wasting disease or to some psychological hazard. It may even reveal a failure of adaptation to some environmental handicap encountered in utero during the early stages of differentiation of cells or organ formation. It seems probable that with so-called hereditary diseases the defect is at the level of gene or enzyme which failed to make a sound adaptation to its environment.

The second rather naive question is, what is our goal in the treatment of a sick child. The general principle underlying all treatment would seem to be that we should help the child to reassert his own immense potential for adaptation until he is no longer "dis-eased." So far as is possible the physician aims at restoring the child to the state of easy comfortable equilibrium, but the old Aesculapian motto "We dress the wounds. God heals them" is still worthy of contemplation. To be sure, treatment may frequently involve removal of an injurious agent from the child's immediate environment. However, a knowledge of how a given child develops good adaptive ability during growth may suggest the desirability of putting major effort into helping the child learn how to adapt to the environment. A child of 7 or 8 years with rheumatic heart disease may serve to illustrate this point in simplest terms. One can make his environment so safe and protecting that he needs to make no exertion which will tax his heart and so that the chance of recurrent infection is minimized. In the long run, however, one will find that many such children will be given a better chance of future health and happiness if one starts helping them to build up their various adaptive mechanisms with graded exercises, adequate diet, and education about the nature of their illness. In the dynamic process of growth even the heart damage may be reduced to a state of relative unimportance. At this point one might note that the thoughtless administration of antibiotics to every child with a common respiratory infection reveals an unfortunate lack of understanding of the process of growth, development, and adaptation. The study of growth teaches the physician to think in long-time terms—teaches him to look ahead over the years rather than just over the next few days or weeks.

If, then, one considers the practice of Pediatrics as being essentially concerned with treating sick children, it is apparent that this always involves some aspect or mechanism of adaptation of the organism. But this organism is a growing child in whom the adequacy of adaptation is dependent upon the active and constantly changing processes of growth, of differentiation, and of maturation. The efficiency of the adult's adaptive mechanisms, in many instances, is dependent upon his own childhood experiences during development. In addition, it is the very nature of the growth process which enables the child to adapt to some circumstances to which the adult organism is unable to adjust. This is one of the joys of practicing medicine with children. It also challenges the pediatrician to be sure he does not thwart the development of adequate adaptive mechanisms

through unwise therapy. Surely the wise pediatrician encourages it by sound treatment. This brings me to a broader defining of Pediatrics.

I believe that Pediatrics is that division of medical science which deals with, first, the positive promotion of healthy growth in individual children from birth through adolescence, second, the prevention of avoidable diseases during this period of growth and development, and third, the treatment of sick children. I believe the pediatrician should be able to profess special study, skill, and understanding in order to help communities, parents, and the children themselves to accomplish these ends.

If you accept some such liberal and idealistic defining of the functions and responsibilities of today's pediatrician you will follow the concept to its logical conclusion. We can hardly expect to educate physicians to carry out such functions without including as much as we can teach them about the nature of biological and, particularly, of human growth. Unless we do this we have no right to expect the physician to be wise in helping the child to attain his maximum potential as a healthy adult. It is apparent, then, that the disciplines of Pediatrics and of Human Growth are very closely related.

One might even inquire whether there is any significant distinction between the two as I have been defining them. As fields of knowledge there is obviously much in common, but the study of human growth is somewhat broader and more inclusive, embracing parts of genetics, anthropology, psychology, and sociology as well as the basic medical sciences. There is, of course, another and more dramatic difference. Pediatrics is a clinical science in which the primary responsibility is to practice what is known for the benefit of children. Its responsibility for acquiring new knowledge through research is always dependent upon and related to this primary goal of promoting health and happiness in children. By contrast, the science of Growth and Development is not primarily a clinical field—it is the physician, the teacher, the clinical psychologist, the nurse, the social worker, and the parents who put into practice the knowledge gained in this area. Moreover, the primary purpose for application of its newly found knowledge is to be found in the wiser and more enlightened guidance of individuals during growth so that they may enjoy a healthy adult life with balance and integrity. The emphasis of those who are absorbed in the broad field of human growth is on the whole human life span, the pediatrician's, on childhood.

In closing, may I return to my original suggestion that Pediatrics as a field of knowledge is essentially a subdivision of the broader discipline called Human Growth. I might have phrased this differently. The science of Biology, of which human biology is part, is concerned with the whole span of growth, with reproduction, with development, and with adaptation whether good or bad for survival. Medicine as a field of knowledge is essentially the field of Human Biology. In the clinical application of Human Biology Pediatrics is distinctive because it deals with the individual human organism during the years of rapid growth and development. Moreover, these are the years when the pattern of adaptations being established in each individual may well determine the future health and happiness of that person for life.

Such considerations lead to the conclusion that Pediatrics is one of the most important branches of Medicine or of Human Biology. I have tried to show that the study of Pediatrics and that of Human Growth are inseparable; that Pediatrics is dependent upon knowledge, experience, and wisdom gained by a study of biological growth, and that this discipline is dependent upon pediatricians for application of such knowledge which will, in turn, increase our understanding of the growth of individual human beings. This is why I feel so strongly that the theme of human growth and adaptation should run like a golden thread throughout the years of medical education. And, finally, this is why I believe that Pediatrics holds a key position in planning for the adequate education of the physician.

The Hypothyroid Infant and Child

Therapy with Sodium *l*-Thyroxine

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This communication reviews problems of diagnosis and therapy of hypothyroidism in infancy and childhood and presents 12 representative cases treated with sodium *l*-thyroxine.

Pessimism in regard to treatment and prognosis for children with congenital athyrosis is based upon the high incidence of persisting deficits of intellect and skeletal growth which follow seemingly adequate replacement therapy.

Selected experimental observations made in this laboratory regarding the physiologic role of thyroid in the growth and metabolism of I^{131}-thyroid-ablated infant rhesus monkeys contribute to an understanding of clinical and metabolic features exemplified by these patients. In the athyroid infant monkey, as in the patients to be presented, it has been observed that many metabolic and clinical signs of thyroid deficiency may be controlled with doses of sodium *l*-thyroxine significantly smaller than those required to promote optimal central nervous system and skeletal growth and maturation.* This seeming discrepancy in tissue response no doubt relates to features of distribution and decay of sodium *l*-thyroxine which have been observed in these animals. Available sodium *l*-thyroxine ultimately assumed a volume of distribution equal to that of body water. The time required for this distribution is only twice that required for biologic degradation (utilization). More specifically, in two days, one-half of a given dose of sodium *l*-thyroxine will have become distributed to peripheral tissues, and, of this, more than one-half will have been utilized. In addition, the rate of utilization by an organ system does not vary with metabolic needs or quantity of hormone present.[4]

Threshold requirements of tissues (including liver, muscle, and skin) appear to be met adequately with the smaller doses, whereas larger doses are required to permit an adequate central nervous system and skeletal response.

It is well known that central nervous system growth and development in human infants is particularly critical in the postnatal period. One-half of all postnatal brain growth has occurred by the end of the first year, and about three-fourths of this by the age of six months. Inadequate supply of thyroid hormone will have its most marked effect during this period. In contradistinction to delay in skeletal development, central nervous system defects are seemingly irreversible.

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* References 1-5, Crane, J. T., and Pickering, D. E.: Central Nervous System Development in Thyroid-Ablated Infant Rhesus Monkeys—Untreated and Treated with Sodium *l*-Thyroxine, unpublished data.

Initial therapy in the congenitally athyrotic infant must be directed toward supplying sufficient thyroxine for early critical central nervous system and skeletal development. To accomplish this, exogenous hormone must be supplied to replace exhausted transplacentally acquired stores which have maintained the fetus in utero. This exhaustion is manifest by signs of deficiency within three to six weeks. Uncertainty in evaluation of long-term effects of replacement therapy in congenital athyrotics, as regards central nervous system development, will persist until such time as a significant group of these infants are adequately treated from this early age.

The preparations available for replacement therapy include desiccated thyroid, *l*-thyroxine, and *l*-triiodothyronine. The variable composition of desiccated thyroid and its tendency to produce toxicity, even when given in less than adequate amounts, are limiting characteristics—especially with its use in infancy and early childhood.

Thyroxine was first isolated by Kendall, in 1915,[6] and subsequently synthesized by Harington, in 1926-1927.† It has been extensively investigated for clinical and metabolic effects over the past three decades.‡ The levorotatory isomer has been found to be most active metabolically,§ and orally it is most effectively absorbed as the sodium salt ‖ (approximately 70% is absorbed following oral administration).¶ All major clinical and metabolic signs of hypothyroidism are reversible with administration of sodium *l*-thyroxine.#

As compared with desiccated thyroid, sodium *l*-thyroxine has a more predictable effect on serum hormonal iodine and basal metabolic rate.* The ability of thyroxine to suppress thyroid-stimulating hormone (TSH) output by the pituitary has been well established.†

Effects of sodium *l*-thyroxine on growth and development of the hypothyroid child, however, except for the limited study of Salter and Rosenbloom,[22] have not been previously reported, though ability of sodium *l*-thyroxine to maintain a normal rate of growth and development in the athyroid infant monkey has been established.‡

l-Triiodothyronine, recently isolated and synthesized by Gross and Pitt-Rivers,§ has been shown to constitute a small percentage of the thyroxine content of thyroid and plasma and to be qualitatively similar to thyroxine in its action on tissue respiration, goiter prevention, and secondary clinical and biochemical signs of hypothyroidism. Moreover, limited in vitro studies have shown thyroxine and triiodothyronine to be similar in their effect on tissue respiratory enzyme systems.‖ Because *l*-triiodothyronine has a more rapid and pronounced initial effect, it has been considered to be 3 to 10 times more potent than *l*-thyroxine.¶ The maximum clinical response with *l*-triiodothyronine occurs in approximately one-quarter the time, and the half-life value is considerably shorter than that for sodium *l*-thyroxine.# This more rapid and intense effect, however, is dissipated over a proportionately shorter period.* On an equimolar basis, the overall calorigenic effect appears equal.

l-Triiodothyronine, in quantities sufficient to cause suppression of I^{131} uptake by thyroid in normal adults, causes transient lowering of serum hormonal iodine, whereas sodium *l*-thyroxine produces no change, or a slight rise.[29] Moreover, toxicity is manifest with

† References 7 and 8.

‡ References 1-5 and 9-36; Crane, J. T., and Pickering, D. E.: Central Nervous System Development in Thyroid-Ablated Infant Rhesus Monkeys—Untreated and Treated with Sodium *l*-Thyroxine, unpublished data.

§ References 12-14, 17, and 18.

‖ References 11, 16, and 19.

¶ References 16 and 22.

References 9-12, 17, 20-23, 27, 28, 30, 31, and 36.

* References 4, 16-18, 21-23, 28 30, 31, and 36.

† References 13-15, 19, 20, and 29.

‡ References 1, 2, 5, 34, and 36.

§ References 37-42.

‖ References 25-27.

¶ References 23, 26-31, and 36.

References 4, 27, 28, 30, 31, 33, 36, and 39.

* References 27, 28, 30, 32, and 36.

l-triiodothyronine in doses of 4 to 10γ kg.,† while considerably greater quantities of sodium *l*-thyroxine are required to produce toxicity.‡ Similar observations regarding toxicity have been made in the athyroid immature monkey where that compound (*l*-triiodothyronine), when given in quantities sufficient to produce growth, was observed to produce profound toxicity in contrast to equimolar doses of *l*-thyroxine, which produced an equal or better growth response without toxicity.§

Serial serum hormonal iodine determinations as a guide to therapy, while of value with sodium *l*-thyroxine or desiccated thyroid, would be of little value with *l*-triiodothyronine, since serum protein does not bind *l*-triiodothyronine as efficiently as it does sodium *l*-thyroxine,[24] and serum hormonal iodine values during administration of *l*-triiodothyronine are low.‖

CLINICAL MATERIAL AND METHODS

The children reported in this communication have been observed in the Pediatric Endocrine and Metabolic Clinic of the Department of Pediatrics of the University of California Medical Center during the past three years. Among 30 hypothyroid infants and children treated with sodium *l*-thyroxine during this time, 12 who are particularly representative of the problems encountered in diagnosis and therapy are presented. Case histories appear in abstract form and are divided into two groups: (1) six infants and children under 4 years of age; (2) six older children.

Laboratory studies of these children have included psychometric examination,¶ roentgenographic evaluation,# and I^{131} uptake studies* before and following TSH administration.[43] Values quoted represent 24-hour uptake of a carrier-free dose (50-150μc) of I^{131}. Serum hormonal iodine determinations are reported either as protein-bound iodine (University of California laboratory modification of method of Salter and McKay [44]) or as butyl-extractable iodine (Dr. E. B. Man, Yale University [45]). Specimens during therapy were drawn approximately 24 hours after the last dose of administered hormone (desiccated thyroid or sodium *l*-thyroxine). Other varied chemistries and studies are reported with individual cases. All cases were treated with sodium *l*-thyroxine,† and the dose was administered orally once daily as 0.05 mg. or 0.1 mg. tablets.

GROUP I—INFANTS AND CHILDREN UNDER FOUR YEARS OF AGE

CASE 1 (R. S.).—This boy was first referred to the University of California Hospital at the age of 5 months with the tentative diagnosis of congenital heart disease and associated anemia which had been treated on two occasions by transfusion. Symptoms of pronounced respiratory distress and cyanosis were accompanied by other uninterpreted classical signs of cretinism—including obstinate constipation, difficult feeding, poor growth and development, umbilical hernia, carotenosis, macroglossia, cretinoid facies, dry thickened skin, generalized hypotonia, and dwarfing. There was marked developmental retardation, and bone age was that of a newborn infant. Serum hormonal iodine measured 2.9γ per 100 cc., and there was no uptake of I^{131} by the thyroid, either before or following TSH administration.

During one month of therapy with sodium *l*-thyroxine (0.1 mg/day), nearly all signs of cretinism disappeared; however, this medication was not given for five months thereafter.

He was next seen at the age of 11½ months, again a classical cretin. He had erupted no teeth, and the skeletal age was 3 months. Serum hormonal iodine was 2.4γ per 100 cc., and serum cholesterol was 133 mg. per 100 cc. He was again given sodium *l*-thyroxine and again experienced a rapid reversal of signs and symptoms of cretinism. He has shown no toxicity on the following dosage schedule:

Sodium *l*-Thyroxine Dosage, Mg./Day	Duration of Treatment, Mo.	Serum Hormonal Iodine, γ/100 Cc.
0	...	2.9
0.1	2½	7.2
0.15	5	7.2
0.2	8½	12.2

During the first 16 months of treatment his length has increased optimally; his dental age has been within normal limits since the age of 1½ years,

† References 23, 24, 26-28, 30, and 31.

‡ References 10, 12, 17, 21-23, 27, 28, 30, and 31.

§ References 1 and 2; Pickering, D. E., and Fisher, D. A.: Growth Effects of *l*-Thyroxine Versus *l*-Triiodothyromine in Athyroid Infant Rhesus Monkeys, unpublished data.

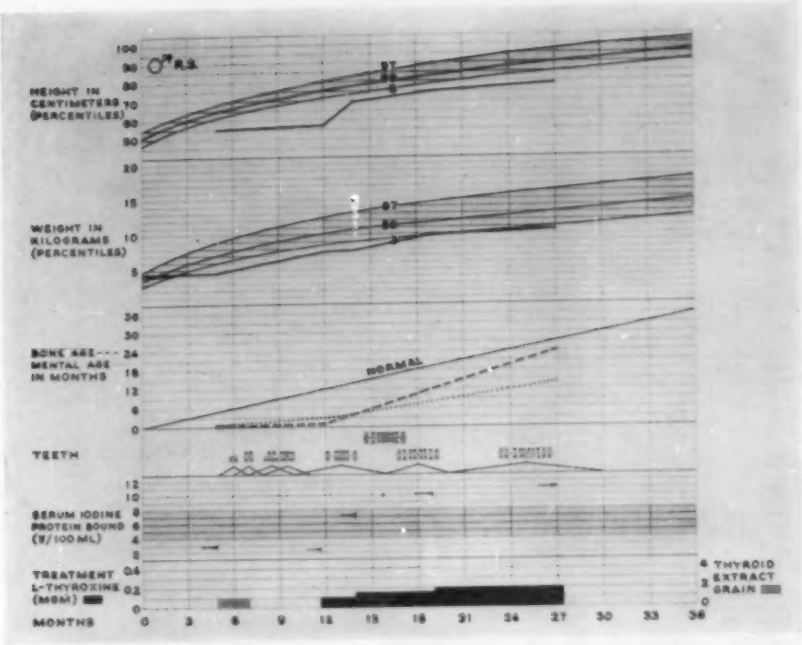
‖ References 23, 27, 29-31, and 36.

¶ Performed in the Pediatric Mental Health Unit, by D. Harvin and R. Smith, psychometrists.

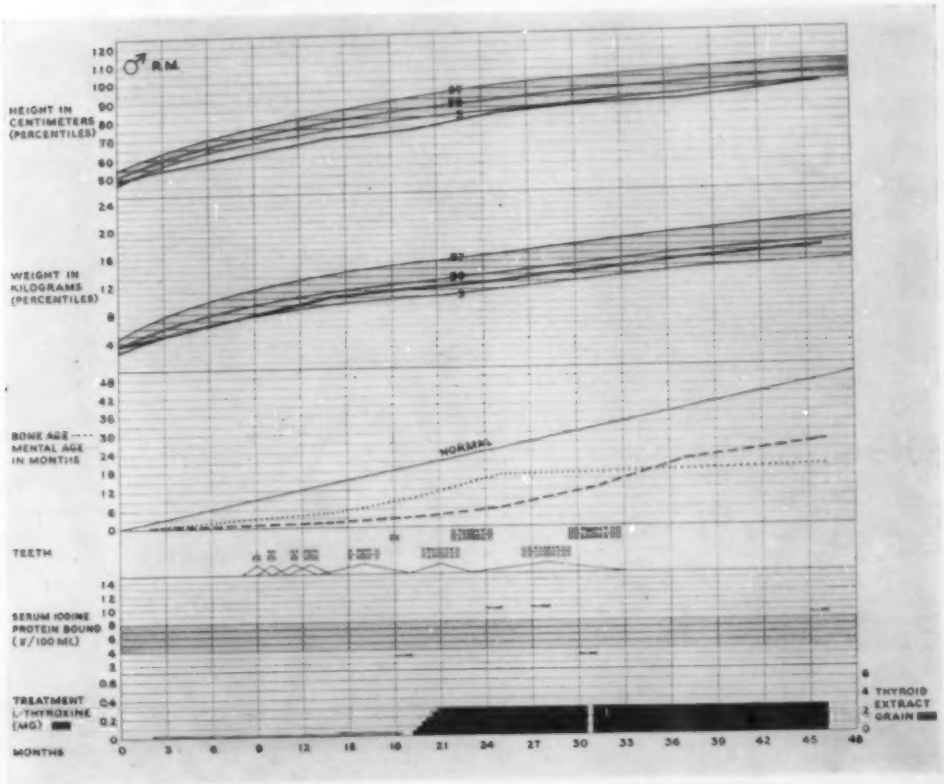
All films were evaluated by Dr. L. B. Lusted, Department of Radiology, University of California Medical Center.

* With Dr. E. R. Miller, Department of Radiology, University of California Medical Center.

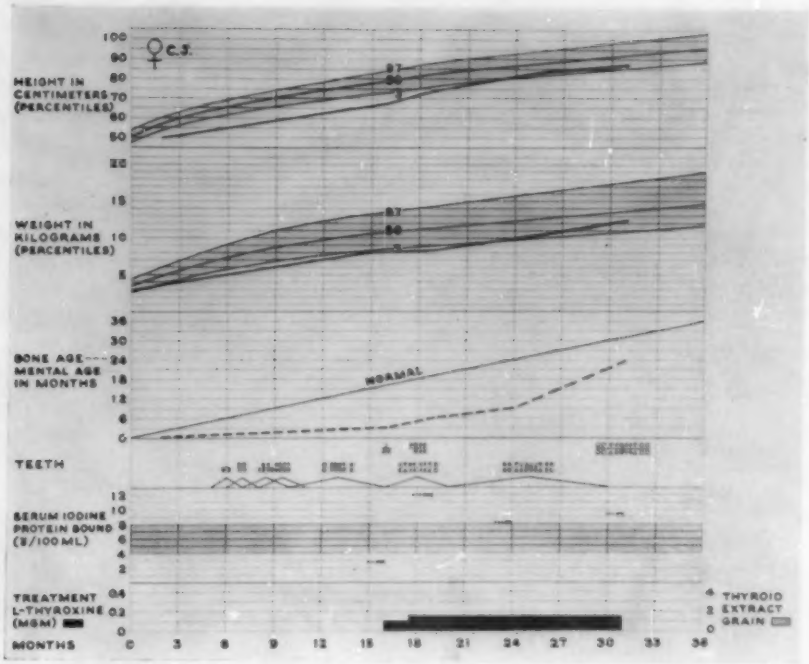
† Sodium *l*-thyroxine (Elthrin) used in these studies was supplied by Smith, Kline & French Laboratories.



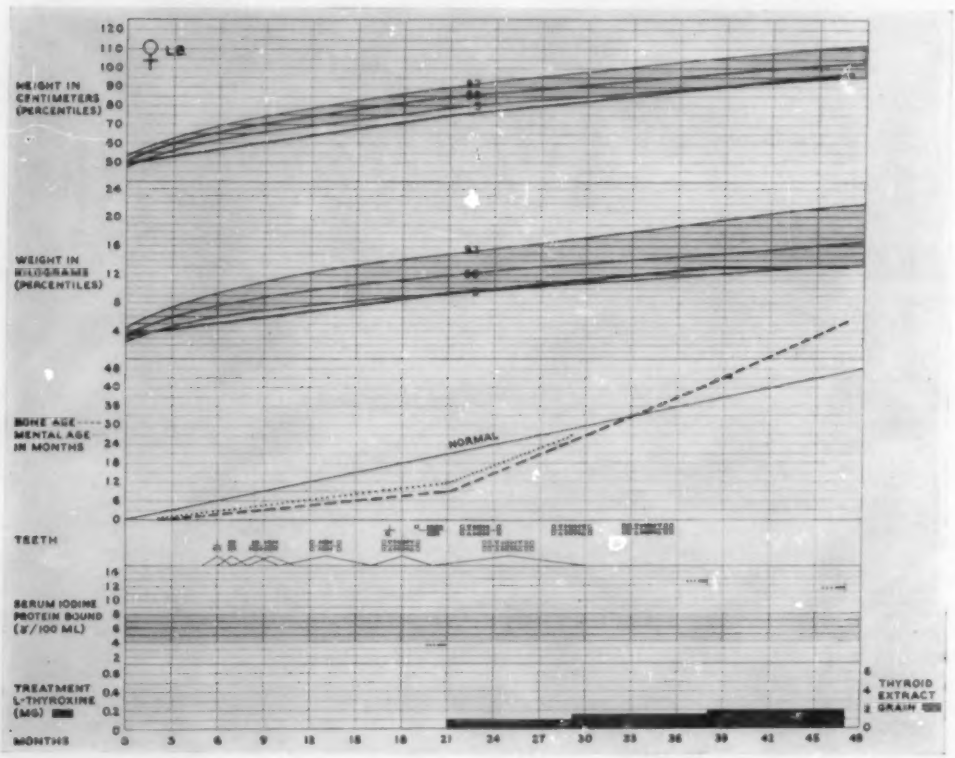
Graph 1.—Summary of growth and treatment data on Case 1 (R. S.).



Graph 2.—Summary of growth and treatment data on Case 2 (R. M.).



Graph 3.—Summary of growth and treatment data on Case 3 (C. J.).



Graph 4.—Summary of growth and treatment data on Case 4 (L. B.).

and his bone age has advanced 17 months. Severe mental retardation has persisted. Data relating to growth and therapy are presented in Graph 1.

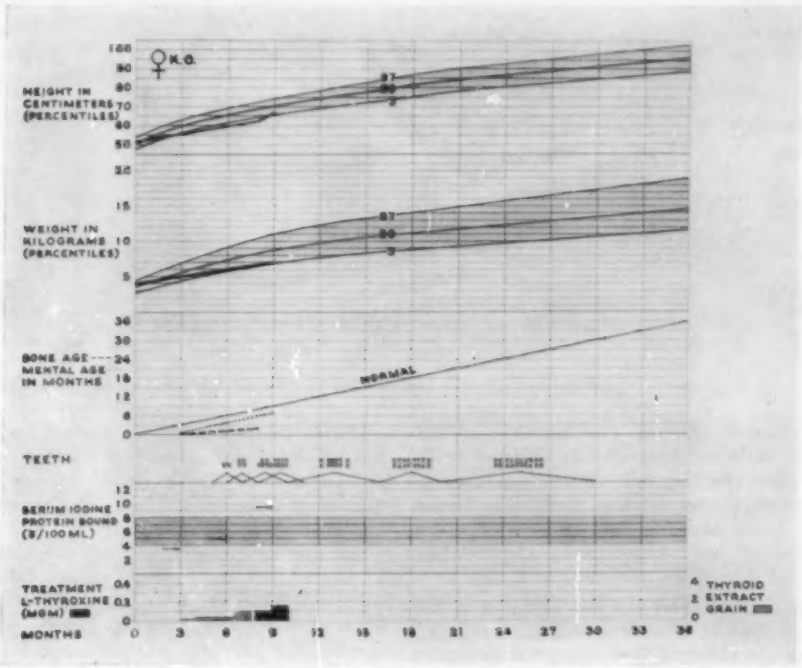
Case 2 (R. M.).—This boy was first seen at this clinic at the age of 18 months. Cretinism was diagnosed during his second month of life, when he presented severe respiratory distress with intermittent cyanosis, macroglossia, thickened dry skin, umbilical hernia, anemia, obstinate constipation, and subnormal temperature. Bone age was that of a newborn, and serum cholesterol was 104 mg. per 100 cc.

Between the ages of 2 and 18 months, he was treated with desiccated thyroid (¼ to ½ grain [15 to 30 mg.] per day). After a short interval without desiccated thyroid, his serum hormonal iodine level was 3γ per 100 cc., skeletal age 3 months, serum cholesterol 140 mg. per 100 cc., and serum carotene 517γ per 100 cc. A subnormal uptake of I^{131} was not significantly altered by TSH administration. His developmental age was 10 months.

He has subsequently received sodium *l*-thyroxine (0.2 to 0.3 mg/day). He began walking three months after institution of therapy, and after four months of treatment 14 deciduous teeth had erupted. During 27 months of therapy, his bone age increased by 24 months and growth was optimal. Mental retardation has persisted. He has shown no signs of toxicity. Three serum hormonal iodine determinations on 0.3 mg. of sodium *l*-thyroxine per day were 9.4γ, 9.5γ, and 8.5γ per 100 cc.

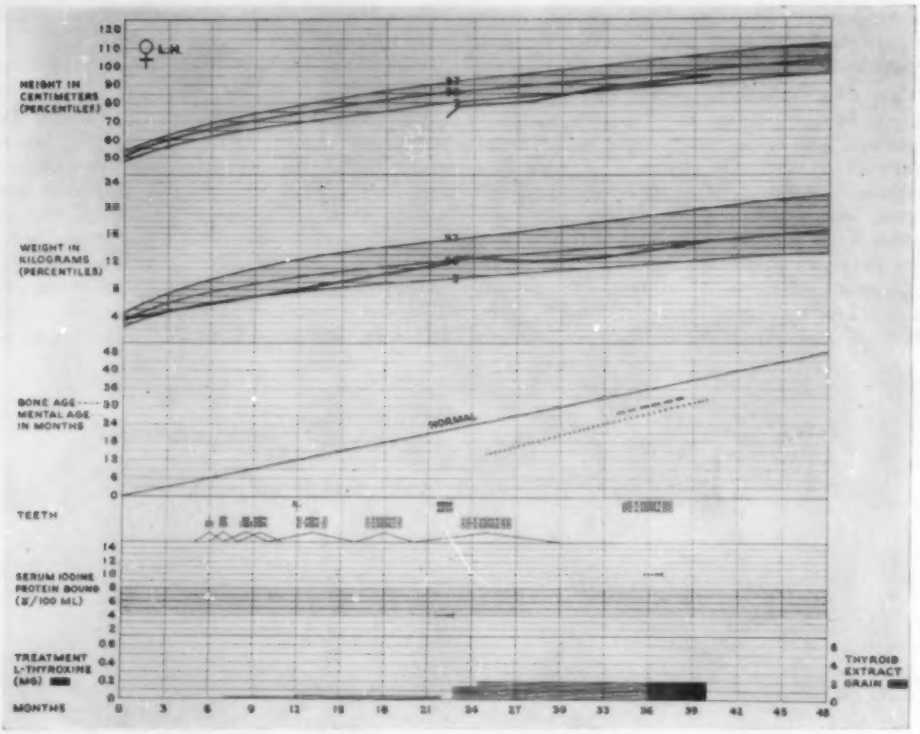
Data relating growth and therapy are presented in Graph 2.

Case 3 (C. J.).—This female cretin was first seen at this clinic at the age of 16 months. At one month she was lethargic and hypotonic, would not feed, had a weak cry, and had developed carotenosis. With progression of feeding difficulty and marked respiratory distress, she was hospitalized at the age of 2 months, with the tentative diagnosis of tracheoesophageal fistula. Though attending physicians described classical edema of her face, tongue, and neck, obstinate constipation, and anemia, the definitive diagnosis was not made. She remained an undiagnosed problem until the age of 16 months. At that time she presented continuing anorexia, constipation, carotenosis, hypotonia, macroglossia, umbilical hernia, myxedema, and retarded growth and development.



Graph 5.—Summary of growth and treatment data on Case 5 (K. O.).

Bone age was 3 months, serum hormonal iodine was 2.8γ per 100 cc., and serum cholesterol was 188 mg. per 100 cc. There was an insignificant 24-hour uptake of I^{131} by the thyroid, which did not increase with TSH administration. Therapy with sodium *l*-thyroxine was instituted (0.15 mg/day) and has continued (15 months) without evidence of toxicity. After one month of therapy, nearly all physical signs and symptoms of cretinism



Graph 6.—Summary of growth and treatment data on Case 6 (L. H.).

had disappeared. During this period, she has grown optimally and bone age has advanced to 24 months. Her dentition has advanced to normal. Mental retardation has persisted (I. Q. 40). Serum hormonal iodine determinations on three occasions were 11.9γ, 8.2γ, and 9.4γ per 100 cc. Data relating growth and therapy are presented in Graph 3.

Case 4 (L. B.).—This girl was first seen at this clinic at the age of 21 months because of retarded growth and development (first detected at the age of 5 months). In addition, she manifested carotenosis, lethargy, constipation, and myxedema. Bone age was 9 months; dental age was approximately 15 months. Serum carotene was 1448γ per 100 cc., and serum cholesterol was 516 mg. per 100 cc. Her 24-hour I^{131} uptake was 12% and did not increase significantly with TSH. Her serum hormonal iodine was 3.6γ per 100 cc.

Therapy with sodium *l*-thyroxine was begun at 21 months and has proceeded as follows without toxicity:

Sodium *l*-Thyroxine Dosage, Mg./Day	Duration of Treatment, Mo.	Serum Hormonal Iodine, γ/100 Cc.
0.1	8	....
0.15	9	12.6
0.2	9	11.6

During the first month of therapy her appetite and activity promptly improved, and her myxedema and carotenemia rapidly cleared (serum carotene dropped to 247γ per 100 cc.). Her serum cholesterol dropped to 150 mg. per 100 cc. At 21 months of age (before therapy), her mental age was 12 to 15 months, and at 29 months of age (after seven months of therapy), it was 25 to 29 months, with a Stanford-Binet I. Q. of 100. By the age of 38 months, her bone age had advanced to approximately 42 months, and by the age of 47 months it approximated 60 months. Dosage has subsequently been reduced to 0.2 mg. per day. Data relating growth and therapy are presented in Graph 4.

Case 5 (K. O.).—This female cretin was first seen at this clinic at the age of 8 months. By age 2 months she had demonstrated negligible growth, respiratory distress, macroglossia, umbilical hernia, carotenosis, constipation, hypotonia, lethargy, and dry cold mottled skin. At 3 months her bone age was that of a newborn infant, serum cholesterol was 240 mg. per 100 cc., and serum hormonal iodine was 3.5γ per 100 cc. She received desiccated thyroid (¼ to ¾ grain [15 to 45 mg.]/day) over a five-month period. Serum hormonal iodine on ½ grain (30 mg.) of desiccated thyroid per day was 5γ per 100 cc.

At the age of 8 months, her skin and hair appeared normal and there was no evidence of macroglossia or umbilical hernia. Growth, however, had remained deficient, and her bone age was 2 months. Psychometric examination revealed a developmental quotient of approximately 75.

Therapy with sodium *l*-thyroxine was instituted (0.1 mg. per day), and during the initial month of therapy she experienced increase in appetite, progression in neuromuscular development, and increase in length of 2.5 cm. Serum hormonal iodine determination on that dosage was 9.4γ per 100 cc. She remains on 0.15 mg. of sodium *l*-thyroxine per day without evidence of toxicity. Data relating growth and therapy are presented in Graph 5.

Case 6 (L. H.).—This white girl was first seen at this clinic at the age of 22 months. Cretinism had been diagnosed at age 2 weeks, when she was hospitalized for surgical repair of her umbilical hernia. Carotenosis and anemia were present at that time. She was treated with desiccated thyroid (¼ to ⅜ grain [15 to 22.5 mg.]/day) until age 22 months, when admission here revealed umbilical hernia, dry, thickened skin, constipation, anemia, carotenosis, macroglossia, cretinoid facies, generalized hypotonia, and lethargy. Growth and development were retarded, and only eight teeth had erupted. Serum cholesterol was 194 mg. per 100 cc. Serum hormonal iodine was 3.9γ per 100 cc., and bone age was 6 months. Psychometric testing at 25 months revealed a mental age of about 14 months.

At 23 months, desiccated thyroid dosage was reinstituted at 2 grains (120 mg.) per day and continued 13 months. Clinical evidence of hypothyroidism rapidly disappeared, and by 28 months she was able to stand alone and feed herself. Growth accelerated during this period, and by 36 months her normal complement of teeth had erupted and her bone age had advanced to 30 months. There was no evidence of toxicity on this increased dosage.

Since age 36 months she has received sodium *l*-thyroxine (0.2 mg. per day) without toxicity. Serum hormonal iodine on this dosage was 10.0γ per 100 cc. Over the first four-month period on this therapy, her length increased an additional 4.5 cm. and her weight an additional 2 kg.

At 32 months of age her mental age was 24 months (I. Q. 75), and at 40 months of age her mental age was 32 months (I. Q. 80). Data relating growth and therapy are presented in Graph 6.

COMMENT

(Cases 1-6).— Despite early manifestations of hypothyroidism in these six cases, the diagnosis was delayed in three of the six for 5 to 21 months. Respiratory distress was a striking early sign. The key to early diagnosis in this age group singularly rests upon a high index of suspicion on the part of the attending physician when any of the classical signs or symptoms are manifest.

The accurate determination of serum hormonal iodine concentration has represented a valuable laboratory aid to diagnosis in this age group. Pretreatment values in these cases ranged from 2.4γ to 3.9γ per 100 cc. Normally, serum hormonal iodine concentration in the neonatal period is considerably above the usually accepted adult minimum standard of 4γ per 100 cc. and after three months ranges from 4.5 to 8.5γ per 100 cc.§

Delay in skeletal maturation was observed in all cases. Though time is required to accumulate a significant deficit, bone age evaluation is felt to be of diagnostic value by the time clinical signs are manifest.

Hypercholesteremia, a common finding in older children and adult hypothyroid patients, was observed in only one of these six cases.

Carotenosis was present in all patients, and carotenemia was confirmed in the two cases where this determination was carried out. I^{131} uptake by thyroid before and following TSH confirmed the diagnosis of primary hypothyroidism in patients tested (Cases 1-4).

Treatment of these cases (Graphs 1-6) points out the efficacy of sodium *l*-thyroxine as well as many important features differentiating adequate from inadequate therapy. In three cases (2, 5, and 6) diagnosed relatively early (2 weeks to 3 months), adequate treatment was delayed for 8 to 24 months. The superficial response in these cases to small doses of desiccated thyroid seemed satisfactory to attending physicians and parents. However, growth and developmental stigmata of inadequate therapy gradually became obvious. Though a detectable increment in body length did occur over that period, deficits persisted, particularly in the areas of skeletal maturation and central nervous system development. Delay in eruption

§ References 46 and 47.

of deciduous teeth with inadequate therapy roughly paralleled the lag in skeletal development.

In five of the patients presented, adequate therapy was not instituted sufficiently early to avoid irreversible mental retardation. With institution of adequate doses of either desiccated thyroid (Case 6) or sodium *l*-thyroxine (all cases), rapid clearing of remaining clinical signs of the disorder and a prompt acceleration of skeletal growth and maturation associated with accelerated eruption of deciduous teeth occurred.

With administration of 0.1 to 0.3 mg. of sodium *l*-thyroxine daily in these six cases, serum hormonal iodine levels varied from 7 to 12γ per 100 cc. While there was a tendency in the individual patient for predictable increase in serum hormonal iodine with increased dosage and consistency of serum hormonal iodine with a given dose, these tendencies did not hold when applied to the group. Toxicity did not occur even though serum hormonal iodine concentration ranged at or above the upper limits of normal for prolonged periods.

It is interesting to note that Case 4, after 26 months of therapy with sodium *l*-thyroxine in amounts producing a serum hormonal iodine of approximately 12γ per 100 cc., demonstrated a skeletal maturation exceeding her chronological age by approximately 12 months without manifest toxicity. Thyrotoxicosis in childhood is known to be accompanied by varying degrees of advanced skeletal maturation,‖ and thyroid medication has previously been reported to produce similar advanced skeletal maturation with and without manifest toxicity.¶ Moderate decrease in dosage will suffice to control this development.

GROUP II

This group of six older children includes three with congenital athyrosis and three with acquired hypothyroidism. Data relating to one of the athyrotics (Case 9) and one of the acquired hypothyroids (Case 12) are presented graphically.

‖ References 48 and 49.

¶ References 49 and 50.

CASE 7 (J. S.).—This male cretin was diagnosed at the age of 2½ months. Symptomatology and findings at that time included strangulation with eating, deep cry, and hypothermia. His serum cholesterol was 183 mg. per 100 cc., and there was no uptake of I^{131} by thyroid. Therapy with desiccated thyroid was instituted (½ grain [30 mg.] daily) and increased to 1 grain (60 mg.) daily after five months because of persistent physical, skeletal, and developmental retardation. Dosage remained 1 to 1½ grains (60 to 90 mg.) per day until the age of 9½ years, and thereafter 2 grains (120 mg.) per day until the age of 11½ years, at which time he was reinvestigated—this time for a nodular thyroid first noted by the parents four months earlier. Height, weight, and skeletal maturation were retarded approximately two years, and epiphyseal dysgenesis was marked. After a two-week period without therapy, serum hormonal iodine was 2.8γ per 100 cc.; cholesterol, 350 mg. per 100 cc.; B. M. R., —29%; I^{131} uptake, 18%.

Subtotal thyroidectomy was performed, and pathological study revealed "multiple adenomata with atypical atrophy." Postoperatively he was maintained on 1 to 1½ grains (60 to 90 mg.) of desiccated thyroid daily for 23 months. Retarded growth and skeletal development as well as femoral epiphyseal dysgenesis presisted.

He was then placed on sodium *l*-thyroxine therapy and has remained on 0.2 mg. per day to the present. During the first 12 months his bone age advanced 1½ years (from 11 to 12½ years) and epiphyseal dysgenesis disappeared. He has grown optimally and has evidenced no toxicity. Serum hormonal iodine on this dosage was 5.7γ per 100 cc. His present I. Q. is 73.

CASE 8 (R. H.).—This boy was first seen at this clinic at the age of 9 years 9 months because of "hypersensitivity" to desiccated thyroid. The diagnosis of hypothyroidism was first made at the age of 10 months in an Eastern hospital, when he presented with a seven-month history of lethargy, constipation, hoarse voice, umbilical hernia, macroglossia, anemia, and retarded development. No teeth had erupted. His skeletal age was "retarded." Serum cholesterol was 150 mg. per 100 cc. He thereafter received desiccated thyroid (1 grain [60 mg.]/day) for a 5-year period. He appeared normal, and growth was considered adequate during this period of therapy.

The dosage was then gradually increased to 2 grains (120 mg.) per day and was continued at that level for six months. He gradually developed "hyperirritability," weight loss, insomnia, tremulousness, and palpitation. Dosage was reduced to 1 grain per day and was continued until the age of 7 years, when increase was again attempted. Signs of toxicity reappeared when dosage reached 1½ grains per day.

He subsequently tolerated a dosage of 1 grain per day until the age of 8 years 9 months, when toxicity again became manifest. Further reduction of dosage to ½ grain per day did not completely alleviate toxic signs, and therapy was withheld for a period of two months. Signs of hypothyroidism appeared within three weeks, and by the end of this two-month period he was severely myxedematous and carotenosis was prominent. There was no uptake of I^{131} by thyroid at that time. During the succeeding six-month period (before referral to this group), he was maintained on ¼ to ¾ grain (15 to 45 mg.) desiccated thyroid per day, with suggestive toxicity on the higher dosage.

When first seen in this clinic, at the age of 9 years 9 months, he was not overtly hypothyroid, and height was in the five percentile for nine years. Serum hormonal iodine (off therapy five days) was 3.9γ per 100 cc. His bone age was 5½ years.

He was placed on sodium *l*-thyroxine therapy (0.2 mg. per day), and on that dosage serum hormonal iodine measured 8γ per 100 cc. He experienced a 2 kg. weight loss shortly after institution of therapy and has subsequently gained at a normal rate. He has increased his shoe size for the first time in two years, and his linear growth has accelerated. During his first 10 months on sodium *l*-thyroxine therapy, his bone age advanced about one year (to 6½ years).

Case 9 (D. F.).—This boy had been treated for hypothyroidism since the age of 2½ years, when he presented retardation of physical growth and mental development and was anemic.

Between the ages of 2½ and 11 years, he received ½ to 1½ grains of desiccated thyroid daily. Therapy was discontinued at the age of 11 years because of "hyperirritability." He then became less active and gained weight rapidly. He received three 8-week courses of chorionic gonadotropin over an 18-month period, beginning at age 13 years.

He was first seen at this clinic at the age of 14$\frac{5}{12}$ years, at which time retarded linear growth, lethargy, and myxedema were evident. Serum hormonal iodine was 2.7γ per 100 cc., and serum cholesterol was 348 mg. per 100 cc. His bone age was 9 years, and femoral epiphyseal dysgenesis was prominent.

He was treated with desiccated thyroid during the succeeding 15 months. Serum hormonal iodine level on that dosage was 4.4γ per 100 cc. Though his bone age advanced from 9 to 11 years, evidence of hypothyroidism persisted during this period. Linear growth remained deficient, and epiphyseal dysgenesis persisted. Attempts to increase desiccated thyroid dosage were unsuccessful and precipitated tachycardia, hyperirritability, tremor, and diarrhea.

He has subsequently received sodium *l*-thyroxine for a period exceeding two years. Following the initial two-month period on a dosage of 0.4 mg. per day, he has been maintained on 0.5 mg. per day. During his first 20 months on sodium *l*-thyroxine, he has grown 16 cm. and has gained 13.6 kg. His bone age has advanced from 11 to 15 years, and all evidence of epiphyseal dysgenesis has disappeared. Serum hormonal iodine levels on three occasions while on 0.5 mg. of sodium *l*-thyroxine per day varied between 8.1 and 10.8γ per 100 cc. He has shown no signs of toxicity. Data relating growth and treatment are presented in Graph 7.

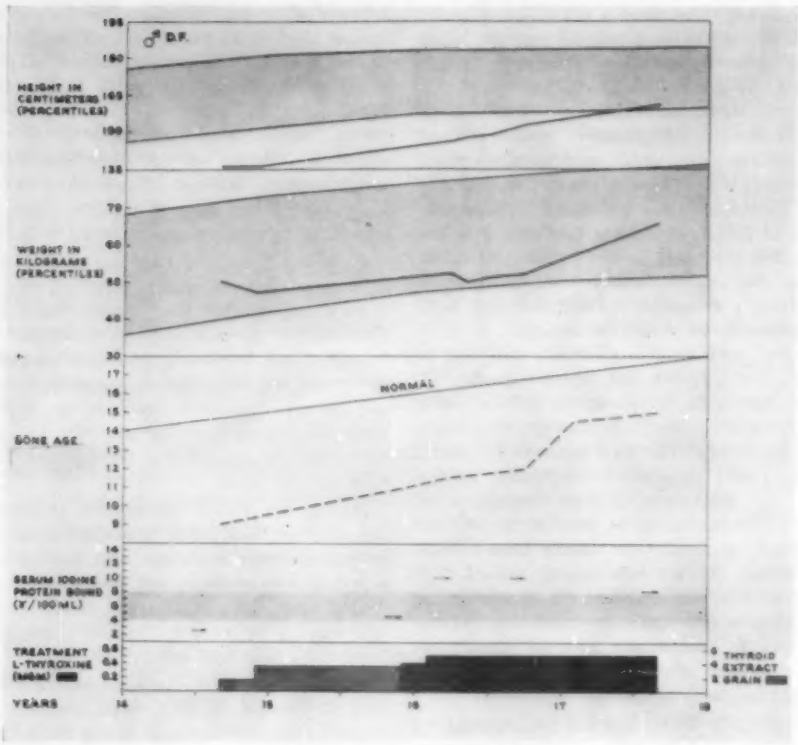
Case 10 (M. G.).—At the age of 8½ years, this girl was investigated for thyroid enlargement known to have been present for the preceding 18 months. Examination revealed a diffusely enlarged nodular thyroid gland. A nearly total thyroidectomy was performed, and pathologic examination of the surgical specimen revealed "Hashimoto's thyroiditis." Until the time of thyroidectomy, she was clinically euthyroid and growth and development had been normal.

During her initial six months postoperatively, she developed cold intolerance, increasing lethargy, increasing dryness of skin and hair, progressive pallor, and carotenosis and demonstrated a 5 kg. weight gain. Twenty-four-hour uptake of I^{131} was less than 5% before and after TSH, and her serum hormonal iodine was 3.5γ per 100 cc.

She has subsequently received sodium *l*-thyroxine (0.2 to 0.3 mg./day). Clinical manifestations of hypothyroidism disappeared during the initial month of therapy. Subsequent growth has been normal, and she has manifested no toxicity. Serum hormonal iodine on 0.2 mg. of sodium *l*-thyroxine per day was 5.8γ per 100 cc., and on 0.3 mg. it was 8.5γ per 100 cc.

Case 11 (J. N.).—This child was first investigated for a thyroid nodule at the age of 7½ years. At that time she was clinically euthyroid. Her serum hormonal iodine was 5.7γ per 100 cc., and her I^{131} uptake was within normal limits. A subtotal thyroidectomy was performed, and a pathological study revealed papillary adenocarcinoma. There was no clinical evidence of local invasion or metastasis.

By 10 weeks postoperatively she had developed dry skin and hair, and her serum hormonal iodine was 3.4γ per 100 cc. Therapy with desiccated thyroid was instituted at ½ grain (30 mg. per day, increased over the succeeding 8 months to 2 grains (120 mg.) per day, and continued for 15 months. At 25 months postoperatively, treatment with 0.3 mg. of sodium *l*-thyroxine per day was begun, and this has continued over a two-year period. On this dose her serum hormonal iodine was 9.5γ per 100 cc. She did not deviate from her normal growth pattern during therapy with desiccated thyroid or sodium *l*-thyroxine, nor has she evidenced toxicity to either drug.



Graph 7.—Summary of growth and treatment data on Case 9 (D. F.).

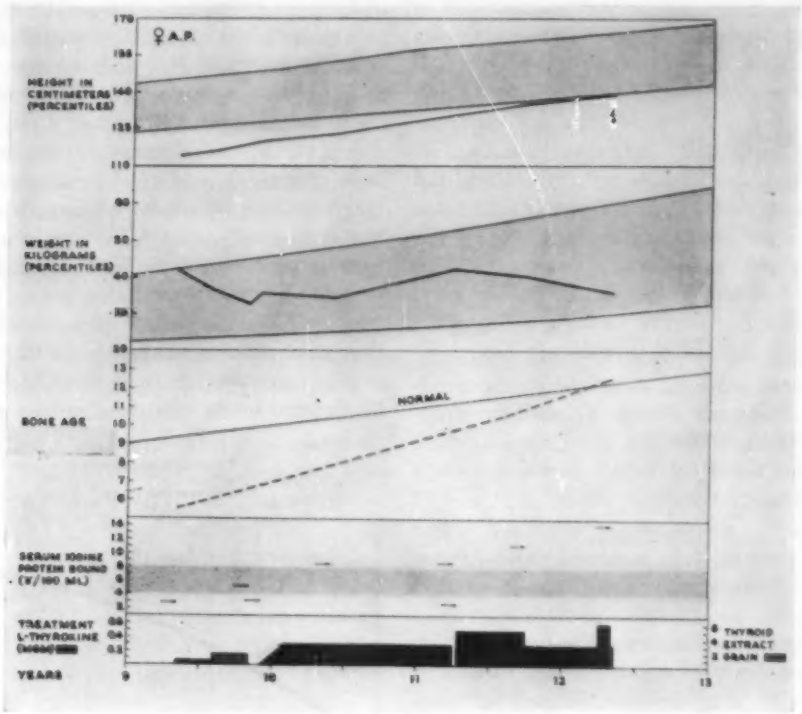
Case 12 (A. P.).—This girl was first seen at the age of 9½ years with symptomatology of hypothyroidism of four and one-half years' duration. Her growth and developmental pattern was normal until age 5 years, when she experienced a precipitous weight gain and gradual development of dry skin and hair following a tonsillectomy and adenoidectomy complicated by prolonged severe respiratory distress and fever. History also included cold intolerance, poor appetite, and occasional dry cough, morning vomiting, marked lethargy, protracted constipation, and retarded linear growth.

At age 9½ years she presented with a height in the 50 percentile for 6 years and was typically myxedematous. Bone age was 5½ years, and serum hormonal iodine was 2.8γ per 100 cc.; cholesterol was 375 mg. per 100 cc., and her B. M. R. was —25%. There was no I^{131} uptake by thyroid before or after TSH administration. Her I. Q. was 107.

She was given desiccated thyroid (1½ grains [90 mg.]/day) for a six-month period. On that dosage her serum hormonal iodine was 5.1γ per 100 cc. Though there was weight loss, increased activity and appetite, and disappearance of nausea and vomiting, clinical evidence of hypothyroidism persisted. After a period of one month without treatment, serum hormonal iodine was 3.0γ per 100 cc., and her serum cholesterol was 271 mg. per 100 cc. Clinical evidence of hypothyroidism was again pronounced.

Therapy with sodium *l*-thyroxine was begun with the dosage schedule and serum hormonal iodine values shown graphically (Graph 8). During this 30-month period of therapy, toxicity has not been manifest and she has experienced an optimal rate of growth. (Over this period she has grown 19.7 cm. and gained 10 kg.) Skeletal maturation, originally retarded four years, is now normal. Growth and developmental data are presented in Graph 8.

Comment (Cases 7-12).—Cases 7, 8, and 9 demonstrated classical signs of thyroid deficiency in infancy. In Case 7, deficiency was manifest by the age of 2½ months, and there followed a nine-year period of inadequate treatment with desiccated thyroid, resulting in shortness of stature, retarded bone age with epiphyseal dysgenesis, and finally, at 9½ years, development of a nodular thyroid which was histologically compatible with



Graph 8.—Summary of growth and treatment data on Case 12 (A. P.).

chronic overstimulation by TSH. Mental retardation persisted.

In Cases 8 and 9 it is interesting to note that deficiency was not manifest during the very early critical period of development. Despite prolonged inadequate therapy with desiccated thyroid, mental retardation is minimal (I. Q. 90+). In these, as in Case 7, however, prolonged inadequate therapy resulted in a slowed rate of linear bone growth and maturation and epiphyseal dysgenesis.

Initial serum hormonal iodine values in these patients ranged from 2.7γ to 3.9γ per 100 cc. I^{131} uptake by thyroid was insignificant and was not increased by TSH in patients so studied (Cases 7, 8, 10, 12). Serum cholesterol values determined during infancy were normal in these cases, as in the earlier group presented, but were elevated in Cases 7, 9, and 12 (348 to 375 mg. per 100 cc.) during later childhood. Carotenosis was not a common feature of hypothyroidism in this older age group.

Treatment.—Desiccated thyroid was utilized as a therapeutic agent in all of these patients. Prolonged periods of inadequate therapy were maintained in four—all of whom demonstrated retarded linear growth and skeletal maturation. There was associated epiphyseal dysgenesis in two and nodular thyroid hyperplasia in one. Two of these six cases demonstrated toxicity to desiccated thyroid in relatively small doses. Therapy with sodium *l*-thyroxine in the amount of 0.2 to 0.6 mg. per day effected and/or maintained a normal rate of growth and skeletal maturation in these six cases.

Cases 7, 8, and 11 have now been treated with sodium *l*-thyroxine for one to two years and Cases 9 and 12 for three to four years. Data relating to treatment response in the latter cases (9 and 12) are presented in Graphs 7 and 8. These cases show the acceleration in linear bone growth and skeletal maturation accompanying institution of adequate therapy.

Serum hormonal iodine values during sodium *l*-thyroxine therapy in these six cases ranged from 5.7γ to 15γ per 100 cc. Though therapy was increased to as much as 0.5 and 0.6 mg. per day, toxicity was not manifest. This is particularly noteworthy in Case 8, where continued treatment with 0.2 to 0.3 mg. per day of sodium *l*-thyroxine (for one year—serum hormonal iodine 8.0γ per 100 cc.) has not caused a recrudescence of sensitivity symptoms, previously pronounced with administration of as little as ¾ grain (45 mg.) desiccated thyroid per day.

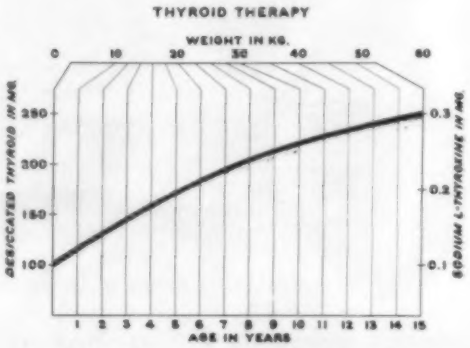
In these patients, as in the younger patients, increased dosage of sodium *l*-thyroxine brought about a predictable increase in serum hormonal iodine concentration—a phenomenon strikingly shown in Case 12 (Graph 8), where serum hormonal iodine values progressively increased from 2.6γ to 14γ per 100 cc. with administration of 0 to 0.6 mg. per day of sodium *l*-thyroxine daily. The consistency in serum hormonal iodine concentration with a given dosage of sodium *l*-thyroxine is again demonstrated in Cases 9 and 12 (on 0.3 and 0.5 mg. per day, respectively).

GENERAL COMMENT AND CONCLUSIONS

In addition to pointing out the relative efficacy of sodium *l*-thyroxine and replacement therapy of hypothyroidism in infancy and childhood, review of these cases emphasizes reliable clinical and laboratory guides to optimal therapy.

In the 12 children presented, sodium *l*-thyroxine satisfactorily reversed physical and biochemical signs of hypothyroidism and promoted normal growth and skeletal maturation. With dosage producing the desired physiologic effect, serum hormonal iodine values ranged above 6γ per 100 cc. In the individual patient these values tended to be constant and predictable with a given dosage.

The determination of serum hormonal iodine concentration as a guide to therapy is of particular value in early infancy, where a rapid appraisal of therapy is essential. It is also of especial value in adolescence, where bone age is a less critical guide. The value of frequent estimation of skeletal maturation as a guide to clinical therapy was emphasized by Wilkins, in 1938,[51] and has been reemphasized by Engeset and co-workers,[52] who made the comment that greater doses are required for skeletal maturation than for linear bone growth. The value of roentgen study in diagnosis and treatment of hypothyroidism has been emphasized by a previous report from this laboratory.[53] While reliance upon clinical and biochemical changes in appearance and/or function of skin, muscle, and liver as evaluation of therapy in the adult is usually adequate, therapy in children must be directed to the relatively greater requirements for skeletal and central nervous system growth and maturation.



Graph 9.—Scale for approximating initial dosage of sodium *l*-thyroxine and desiccated thyroid in treatment of hypothyroid infants and children.

Optimal replacement therapy with sodium *l*-thyroxine (with serum hormonal iodine concentrations ranging from 6γ to 12γ per 100 cc.) has not been observed to be complicated by toxicity. Suggestive early signs of toxicity (widening of the palpebral fissures, mild insomnia, moist palms, increased excitability, and minimal weight loss) have been observed in other cases in this clinic where dosage produced serum hormonal iodine concentration in excess of 12γ per 100 cc.

Considering this wide margin between optimal therapeutic and toxic effects, as well as the consistency of serum hormonal iodine concentration with a given dosage, sodium

l-thyroxine is an espicially efficacious agent for replacement therapy. Applicability of this agent extends also to those cases wherein it is desirable to maintain effective suppression of TSH release by the pituitary (in the postoperative carcinomatous thyroid patients, thyrotoxicosis, thyroiditis, idiopathic goiter, and the goitrous cretin). Moreover, the unusual sensitivity to desiccated thyroid, observed in Case 8, was well controlled with this agent.

Graph 9 presents a scale for approximating the initial dosage of sodium *l*-thyroxine, as well as desiccated thyroid, for treatment of hypothyroid infants and children. This dosage may be approximated on the basis of age and/or weight. Definitive requirements must be determined, however, for the individual case.

SUMMARY

Twelve cases which are representative of the particular problems in diagnosis and therapy of hypothyroidism in infancy and childhood are presented, and results of treatment with sodium *l*-thyroxine are discussed.

The nature and characteristics of principal agents for thyroid replacement therapy are discussed in relation to their applicability in the pediatric age group.

The growth and developmental stigmata of delayed and/or inadequate thyroid replacement therapy in the athyroid infant are emphasized, and the improved response which follows institution of adequate therapy is shown.

The value of serum hormonal iodine levels and skeletal age determinations as diagnostic aids and criteria of adequacy of therapy is illustrated.

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Treatment of the Nephrotic Syndrome with Corticotropin (ACTH) and Cortisone

A Four-and-One-Half-Year Survey of Results with Short-Term Courses

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The effect of corticotropin (adrenocorticotropic hormone [ACTH]) and cortisone on the acute state of the nephrotic syndrome has been described by a number of workers.* That endogenous corticotropin may be responsible for spontaneous remissions is suggested by diuresis following measles and other infections complicating the disease. Also, in one patient whom we observed during the occurrence of a spontaneous remission, we found an increase in urinary cortins and 17-ketosteroids, a fall in eosinophile count and an increase in uric acid-creatinine ratio immediately preceding the diuresis.[4] It is the purpose of this communication to try to evaluate the ultimate value of these hormones when given in short-term courses by reviewing our observations in 64 infants and children who had the nephrotic syndrome and who were treated with either corticotropin or cortisone during the past four and one-half years.

In accordance with a recently proposed classification,[5] no effort will be made to separate children who had the nephrotic syndrome in its so-called "pure form" from those who at one time or another had the disease with hematuria, hypertension, and azotemia. According to this concept, the latter picture represents a stage in the same entity.

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METHODS

Corticotropin was given by the intramuscular route in four divided doses in amounts of 60 to 80 units per 24 hours, usually for 10 to 12 days. When given intravenously, 15 units were given in 300 ml. of 5% dextrose by slow drip over 8- to 12-hour periods. Cortisone was used orally in doses of 150 to 200 mg. per 24 hours in three divided daily doses for 10 to 12 days. When diuresis occurred or if it failed to be noted by the eighth or ninth day, the dosage of the hormones was gradually reduced over a three- to four-day period. During treatment, most children were given a salt-restricted diet and an antibiotic prophylactically. Five to 15 ml. of a 10% potassium chloride solution was given orally daily whenever hypopotassemia became evident; only occasionally was it used prophylactically. Plasma sodium, potassium, and chloride determinations were usually obtained two to three times weekly during periods of treatment. The blood pressure was taken routinely twice daily in all patients. As a rule, nephrotic children were only treated with corticotropin or cortisone when edema and ascites were marked and interfered with the patient's normal activity.

RESULTS

Between October, 1949, and April, 1954, 64 children 1 to 9 years of age came under observation; the shortest period any child has been followed has been 14 months, and more than 50 have been followed for more than 2 years. Sixty-two (97%) were of the white and 2 (3%) were of the Negro race. Twenty-seven (42%) were boys, and 37 (58%) were girls. Major allergies (hay fever, eczema, or asthma) were noted in 7 (11%) of the children. Among 43 patients

TABLE 1.—*Diuresis Induced by Corticotropin or Cortisone During 189 Courses**

	Corticotropin		
	I.M.	I.V.	Cortisone
Number of courses	117	33	39
Over-all incidence of diuresis	.....	81% (153)	.....
Incidence of diuresis	85% (99)	76% (25)	74% (29)
Length of remission in patients treated with 3 or more courses	86 courses—4.2 mo.	.....	22 courses—2.6 mo.
Diuresis beginning during treatment	69% (68)	71% (18)	80% (23)
Diuresis beginning after treatment	31% (31)	29% (7)	20% (6)
Incidence of diuresis in children who subsequently died	53% (17/32)	50% (6/12)	60% (6/10)

* Number of courses is given in parentheses.

in whom eosinophile counts were obtained prior to treatment, 14 (30%) had counts in excess of 500 eosinophiles per cubic millimeter. The family history of 49 of the cases revealed the presence of allergies in sibling or parents in 19 (39%).

Table 1 shows that the over-all incidence of diuresis obtained in our series with either corticotropin or cortisone was 81%. The incidence of diuresis was not significantly different when corticotropin was given by intramuscular or intravenous route or when cortisone was used. The length of remission (time interval between discharge from the hospital and reaccumulation of marked edema) in children treated with 3 or more courses was 4.2 months for 86 courses of corticotropin and 2.6 months for 22 courses of cortisone. However, these data did not lend themselves to statistical analysis.† Table 1 also shows that 71% of the nephrotic children had diuresis during administration of corticotropin or cortisone. Diuresis, occurring after the completion of the course, was noted in 29% of our patients. In 20 children treated with more than three courses, no regularity in the pattern of diuresis was noted. Nine of these patients had diuresis each time while the hormones were administered, and 11 children had diuresis either during or after hormone administration. It is important to note that the incidence of diuresis was definitely lower in children in whom the disease took a progressive course ending in renal failure. The incidence of diuresis was only 54% in this group. It has to be emphasized again that patients with fixed azotemia, persistent hypertension, or creatinine retention were usually not treated with corticotropin or cortisone. The failure of diuresis thus occurred at a time when definite indication of a severe progressive renal disease had not yet appeared. This conclusion also becomes evident from the observation that of 13 patients who failed to have diuresis more than twice during the course of hormone treatments, to date 11 have died of renal failure.

Table 2 shows the corticotropin or cortisone treatments given to 63 patients. It can be noted that 53% received only two courses, 69% only three courses, and 80% not more than four courses of treatment. It seemed of interest to learn whether, in children who were treated with multiple courses, the intervals between courses would become longer as the disease continued. Among 20 children who were treated with four or more courses, the interval between treatments became progressively longer in 2, did not show any regular pattern in 13, and did show a regular pattern in 5.

TABLE 2.—*Number of Courses Given to Sixty-Three Patients*

Courses, No.	Patients, No.	Per Cent Value
1	20	32
2	13	21
3	10	16
4	7	11
5	7	11
6	2	3
7	1	1.5
8	2	3
9	0	0
10	1	1.5

† Our data were reviewed by Dr. George F. Badger, Professor of Biostatistics. The great variability in the length of remissions and the relatively small number of data available did not permit an accurate statistical evaluation.

As far as complications probably referable to the administration of either corticotropin or cortisone are concerned, hypertension with a diastolic pressure of more than 90 mm. Hg was the most frequent, occurring during 22 of 189 courses. It was always reversible and usually did not require interruption of treatment unless associated with signs of impending cardiac failure or convulsive seizures. Hyponatremia was noted in three, hypokalemia in two, and hypocalcemia in two patients. By adjusting the electrolyte and water intake, these deviations were corrected without too much difficulty. The two episodes of hypocalcemia elicited convulsive seizures which were relieved by the intravenous administration of calcium. Convulsions without hypocalcemia were observed four more times in three additional patients. All five patients died ultimately of renal failure. It should be emphasized, however, that in three of these children the convulsive seizures were noted at a time when evidence of a severe functional renal impairment was still missing. While being treated with corticotropin, one 2½-year-old white boy developed a thrombosis of the left renal vein, which ultimately resulted in a small contracted kidney. This child died in renal failure six months after the occurrence of the thrombosis.

In the group of 64 corticotropin- or cortisone-treated nephrotic children, 17 have died (Table 3). Fourteen of these children are known to have died in renal failure. At the time when therapy was first started, 10 of these patients had no hematuria, azotemia, or hypertension. Their disease thus corresponded, according to an older terminology, to so-called "pure lipid nephrosis." Six of these patients received their first course of treatment within one month and two within two months of the onset of their disease. They were treated with three to eight courses, and in eight months to two years after onset they died of renal failure. Table 3 indicates the diminished rate of resulting diuresis (53%) in children whose disease took a progressive course. The incidence of failure of the same child to have diuresis more than twice in this group is striking. It is noteworthy that three children treated within less than one month of the onset of their disease and receiving a total of four

TABLE 3.—*Analysis of Seventeen Fatal Cases*

Status Prior to Treatment *	Duration of Disease Prior to Treatment, Mo.	No. of Treatments	Incidence of Diuresis †	Total Duration of Disease	Time from Last Treatment to Death	Cause of Death ‡	Remarks
P	¼	4	+ + — —	1 yr.	4 mo.	RF + CF	Congenital absence of 1 kidney
P	¼	4	(+) (+) — —	8 mo.	1 mo.	RF	Thrombosis of 1 renal vein
P	½	8	+ + — — + + + +	2 yr.	1 yr.	RF	.....
P	⅝	4	— + — —	1 yr.	5 mo.	RF	.....
P	⅝	3	+ + +	8 mo.	2 mo.	Pancreatitis	Following Escherichia coli peritonitis
P	1	5	+ + + — —	8 mo.	1 mo.	?	.....
P	1⅓	3	— — (+)	2 yr.	7 mo.	RF + CF	.....
P	2	3	+ + —	22 mo.	14 mo.	RF	.....
P	6	2	— —	1⅓ yr.	1 yr.	?	.....
P	7	5	+ + + + +	2⅓ yr.	5 mo.	RF + CF	.....
M	6	1	—	1⅓ yr.	7 mo.	RF	.....
M	7	2	— —	2⅓ yr.	1⅓ yr.	RF	.....
M	7	3	+ — —	3 yr.	6 mo.	RF	.....
M	13	3	+ + —	2⅓ yr.	1⅓ yr.	RF + CF	.....
M	17	2	— —	2⅓ yr.	3 mo.	RF + CF	.....
M	24	1	(+)	3⅓ yr.	15 mo.	RF + CF	.....
M	34	1	+	5 yr.	2 yr.	RF + CF	.....

* P indicates pure form; M, mixed form.
† + indicates diuresis; —, no diuresis.
‡ RF indicates renal failure; CF, cardiac failure.

to five courses of therapy died of renal failure within eight months.

The over-all outcome of the disease is given in Table 4. In addition to the 17 children (26.5%) who died, only one other patient at this time shows evidence of chronic renal disease. His renal status has remained stationary for the last two and one-half years. The 15 children (23%) listed in Table 4 as having the disease in its active form are patients who have been suffering from the nephrotic syndrome for four months to three years in whom edema or ascites was present less than four months before this study was brought to a temporary conclusion. None of these 15 children have, at present, symptoms of progressive renal disease. The 19 patients (30%) listed as in remission are children who have small amounts of proteinuria as the only gross manifestation of the syndrome. Six of these have been in this state for 4 to 12 months, five for 1 to 2 years, and eight for more than 2 years. None of these 19 patients has fixed hypertension, azotemia, or hematuria. Under probably cured, we have listed 12 children (19%) who have been free of all symptoms and findings including proteinuria for more than six months. Three have been in this state from 6 to 12 months, four from 1 to 2 years, and five for 2 to 4 years.

TABLE 4.—*Status of Patients*

	No.	Per Cent
Dead	17	26.5
Chronic renal disease	1	1.5
Active	15	23.0
In remission	19 *	30.0
Probably cured	12 †	19.0
	64	

* 4 mo., 6; 1 yr., 5; 2 yr., 8.
† 6 mo., 3; 1 yr., 4; 2 yr., 5.

COMMENT

The group of children studied reveals again the racial predilection of this renal disease. The low incidence in Negro children is in keeping with previously published observations.[6] It has been pointed out recently [7] that the incidence of allergy seems to be high in nephrotic children. Our data appear to be in agreement, but the number is too small to be conclusive.

The over-all incidence of approximately 80% diuresis is in line with the experiences of others.‡ It is of interest to note that, as far as the incidence of diuresis is concerned, the intravenous administration of corticotropin does not seem to be superior to the intramuscular route. In contradistinction to others,[8] in our study diuresis occurred more frequently (71%) during the administration of these hormones. These findings are in keeping with the observation that diuresis is not the result of hormone withdrawal but is usually caused by hormone alteration of renal function, such as decrease in proteinuria.§ Even though our data do not permit a statistical analysis, they suggest the possibility that the length of remissions may be somewhat longer after the use of corticotropin than after cortisone. This observation is similar to that made by Galan.[11]

Our data show that the length of remissions in patients who eventually recovered did not become progressively longer. They also indicate that the number of courses needed by an individual patient has no important prognostic implication. That 70% of our patients needed only three and 80% needed not more than four courses of treatment indicate that these children did not spend more than a total of one to one and one-half months in the hospital. This figure certainly indicates an impressive improvement in the management of the nephrotic syndrome.

That the incidence of diuresis is lower in children whose disease has progressed to irreversible glomerular lesions is known. It is interesting that failure of diuresis occurred more frequently in these patients even before symptoms of renal failure appeared. The fact that 11 of 13 children who failed to have diuresis two or more times ultimately died in renal failure suggests the

‡ References 1-3.

§ References 9 and 10.

possible prognostic implication of this observation. Convulsions not due to hypocalcemia occurring during treatment may possibly indicate a similarly grave prognosis. The complications that we encountered were few and infrequently required interruption of the courses of treatment.

The evidence of renal vein thrombosis which contributed to the fatal outcome of one patient might be attributed to the hormone administration. Galan,[11] however, has listed several instances of vein thrombosis in nephrotic children who have not been treated with these hormones.

At this point, it might be noted that we do not feel that the appearance of either hematuria, hypertension, or azotemia in itself represents a contraindication to a trial of hormone therapy. The reason for this is that at the present time it seems impossible to know, when these signs first appear, whether the condition is reversible. Therefore, a trial of therapy seems warranted but should be administered cautiously. If it becomes apparent that renal impairment is fixed, hormone therapy is no longer recommended, because the results are poor and the incidence of serious complications is increased.

In a nephrotic population, four and one-half years of observation is not sufficient time to permit a definite statement on the value of a new therapeutic regimen. Certain conclusions may, however, be drawn from our data.

Of the 17 children who died in our series, 10 showed no evidence of hematuria, azotemia, or hypertension when therapy was started. Six of these were treated less than four weeks after onset of the disease, and three deaths due to renal failure occurred within eight months after onset. We believe that these observations suggest that corticotropin or cortisone used as described did not affect the progression of the glomerular lesion. The mortality rate of 26.5% is a value that will show some increase during the coming years in this series. It would appear to us from observation of the course of the disease in the groups listed in Table 4 that our ultimate mortality in this group of patients will probably be approximately 35%.

Although this mortality rate is lower than that reported by some authors, it is in fair accord with results obtained by us in 1946.[9] The impression is gained that corticotropin or cortisone when used in short-term courses does not decrease the mortality rate of the nephrotic syndrome in children. Since we know that these agents may have a beneficial effect, namely, by increasing glomerular filtration rate and urea clearance[12] and by decreasing glomerular permeability for plasma protein[9] and proteinuria,‖ this observation is disappointing. Until further progress has been made, we believe that corticotropin and cortisone have improved the management of these children, that they affect the morbidity of the disease, and that their further use is recommended.

SUMMARY

Sixty-four children suffering from the nephrotic syndrome were treated over a four-and-one-half-year period with 189 short-term courses of corticotropin (ACTH) or cortisone. Twelve (19%) are probably cured. Nineteen (30%) are in remission. In 16 (24.5%) the disease is still active. Seventeen (26.5%) are dead.

Diuresis was obtained in 81%. The incidence of diuresis did not significantly differ whether corticotropin was given by I. M. or by I. V. injection or whether cortisone was used. The average length of remission after corticotropin therapy was 4.2 months and after cortisone, 2.6 months. Seventy to eighty per cent of the children had diuresis while these agents were still being administered. The incidence of diureses in patients who ultimately died in renal failure was 53%. Of 13 patients who failed to have diuresis two or more times, 11 have died in uremia.

Of our patients, 53% needed only one or two courses of treatment; 69% did not need more than three, and 80% needed not more than four courses. Thus, during

‖ References 10 and 13.

their illness, 80% of our patients did not spend more than one to two months in the hospital.

Complications such as azotemia and electrolyte disturbances were infrequent and reversible. Convulsions occurred six times during the period of therapy and were a sign of poor prognosis.

Of 17 children (26.5%) who died, at least 14 died in renal failure. Ten of these had no hematuria, azotemia, or hypertension at the time of onset of treatment. This observation suggests that corticotropin or cortisone given in short-term courses does not affect the progression of the glomerular lesion. An ultimate mortality rate of approximately 35% is expected in this series.

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Prenatal Lesions of the Pancreas

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In order to make the purpose of the experiments to be discussed below clearly understandable, it was thought necessary briefly to summarize the main results of our previous studies concerning the functional pathology of the pancreas.

It has been many years since we first observed that in the first week of scarlet fever the activity of pancreatic enzymes in the duodenal juice becomes decreased and at the same time the level of both amylase and lipase is greatly increased in the blood.[1] After a week this shift characteristic of acute pancreatitis usually disappears. In some instances, however, the pancreatic dysfunction becomes permanent, similarly as after certain cases of mumps or other infectious fevers.* A short time after that observation we had occasion to become acquainted with the morphological basis of the dysfunction: In three patients who died of bacillary dysentery the pancreas presented a picture characterized by degeneration, variably severe necroses, and fibrosis.[4]

Our subsequent experiments were based not only on the above findings but mainly on those made during the siege of Budapest in 1945. It was observed that infants who became ill in consequence of the diet lacking in protein developed steatorrhea as the first clinical sign of the deficiency disease. Since up to that time this phenomenon had not been known to form part of the *Mehlnährschaden* syndrome, we attempted to detect its cause. Thus it was disclosed that at a very early stage of the disease the activity of pancreatic enzymes is in most cases markedly decreased and that with the progression of the disease it completely ceases.† This unexpected finding became fully explainable by finding of cystic degeneration and fibrosis of the pancreas at autopsy,[7] a picture identical with the one subsequently described in kwashiorkor ‡ and in other forms of malnutrition § in which diseases of the enzymic dysfunction is equally present.‖

In order to clarify the cause underlying the above clinical findings, animal experiments were started. It was found that by long-continued administration of toxic substances, such as the endotoxin of Shigella paradysenteriae, chlorinated hydrocarbons, zinc salts, and histamine, just as by feeding a methionine-free diet, it is possible to induce changes in the appearance of the pancreas of albino rats which are similar to those observed in patients who have died of dysentery or in infants who have died of protein-deficiency disease.¶

The fact that the morphological appearance of the pancreas was the same regardless of the factor by which disease was induced made us assume that the change observed represents the general response of the pancreas to all kinds of protracted mild injury.[17]

The single morphological steps during the development of the change, as observed by us and confirmed by several investigators, are the following. (The same changes induced by a methionine-deficient diet may also be produced by inhibiting methionine metabo-

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* References 2 and 3.

† References 5 and 6.

‡ References 8-10.

§ References 11-14.

‖ References 10, 15, and 16.

¶ References 4, 7, and 11.

lism through feeding with ethionine.#) First, the zymogen granules disappear from the supranuclear zone, the perinuclear basophilia diminishes, and the cell stains intensely with eosin. Subsequently, the acinar cells become inflated and vacuoles develop in them from which cysts are soon formed, apparently through the coalescence of several vacuoles. In the meantime, invasion with fibroblasts begins, and extensive fibrosis results from the proliferating connective tissue. The lobule is divided into numerous areas independent of one another by the thickening bundles of connective tissue invading it, and, in consequence of the shrinking, in the degenerated parenchyma, whose original structure has become utterly unrecognizable, there remain very few cells presenting a normal aspect. Within the single lobules the degree of the change is uniform, but different lobules become involved in the process at different times. In this way the pancreas displays a variegated and very unusual picture, neighboring lobules often presenting quite different stages of the change.

The morphological appearance of the fibrotic lobules displaying cystic degeneration is very similar to the usual picture found in the condition, well known in infancy, of cystic fibrosis of the pancreas. The more so as the bronchial change practically always associated with infantile fibrocystic disease is also regularly present in most animals exposed to toxic injury and in many of those fed on a deficient diet, as found by us [2] and corroborated by other authors.[22]

In the light of the observations reviewed, it is only natural that we have attempted to produce experimentally in utero a condition identical with infantile fibrocystic disease of the pancreas, commonly believed to be of hereditary nature.

It was thought that the condition would develop in the young in utero on exposing a pregnant animal to toxic injury or on feeding it on a deficient diet, either in the first third of the pregnancy or during its whole course. First the experiments were performed on rats. These trials remained serially unsuccessful, as the fetuses became absorbed. The most we could attain was that instead of being absorbed they were delivered prematurely, but this was at such an early stage that their pancreas was still undeveloped.[23] Then we began experimenting on dogs. With use of the same procedure as before, no mature offspring could, however, be obtained. The experimental procedure was therefore modified so that the injury, whether toxic or dietary, was not applied before the last stage of the pregnancy. The results of these experiments are reported here.

MATERIAL AND METHODS

Ten pregnant mongrel dogs ranging in weight from 15 to 20 kg. were used. Four of them, serving as controls, were fed a normal well-balanced diet and were exposed to no injury whatever. Three dogs were fed a methionine-free diet, the composition of which was described in a previous paper,[7] and were exposed to no other injury. It was planned to begin with the deficiency diet 14 days before delivery, but one dog brought forth its litter earlier and one later than expected, so that the dietary injury lasted 9, 14, and 20 days, respectively. The three remaining dogs were fed the same diet as the controls and were daily treated with 1 ml. of carbon tetrachloride subcutaneously for 10, 16, and 18 days, respectively.

After delivery, both kinds of injury were immediately discontinued and all the 10 animals fed on the same diet. This consisted of the normal diet previously given to the control animals, with extra milk and meat added. In this way was it intended to avoid inducing some postnatal lesion in the puppies. The puppies sucked their mothers; those surviving six weeks were fed on a well-balanced diet rich in milk.

The puppies of the control bitches were worked up between the ages of 1 and 12 weeks; those of the six experimental animals, in every instance, immediately after their spontaneous death; the experimental bitches, 12 weeks after delivery. Postmortem changes were never observed, and so the findings to be described were held to be suitable for evaluation.

RESULTS

As regards the puppies, the difference between the control group and the two experimental ones was conspicuous from the first moment. The four control bitches brought fourth 24 puppies, all of them seemingly normal and well developed. Of the 25 puppies born of the three animals treated

References 18-20.

with carbon tetrachloride, 12 were born dead; of the 20 puppies of the three animals that were fed a deficient diet, 8 were born dead (Table 1).

The living experimental puppies were, however, not normal. Nothing could prove this more clearly than the fact that within 10 days following their birth 4 puppies died from among the 12 of the carbon tetrachloride group and 9 died out of the 12 of the dietary group. After 20 days, all that remained living were five puppies from the toxic group and a single one from the dietary group (Table 2).

TABLE 1.—*Comparison of Control Group with Experimental Groups*

Experiment	No. Pregnant Dogs	No. of Puppies Born		
		Total	Living	Dead
CCl_4	2	25	12	13
Dietary	2	20	12	8
Control	4	24	24	..

TABLE 2.—*Length of Survival of Puppies of Experimental Groups*

Experiment	No. Puppies Born Alive	Dead		Living	
		Within 10 Days	Within 20 Days	After 20 Days	After 35 Days
CCl_4	12	4	3	5	2
Dietary	12	9	2	1	..

The six puppies surviving 20 days thrived apparently well at the beginning of their life and put on weight almost normally. Soon, however, they developed diarrhea with putty-like offensive feces characteristic of pancreatic failure. At the same time, the animals began to lose weight rapidly, and one to two weeks later they died (Table 2). After five weeks only two puppies were still alive, and after seven weeks, only one puppy. It was on the 83d day that this last experimental puppy died. Bacteriological examinations could reveal in no animal pathological agents responsible for the diarrhea.

Autopsy and microscopical examination of both the experimental bitches and the control puppies revealed perfectly normal organs, including the pancreas (Fig. 1). In the experimental puppies no changes were found except in the pancreas and the lungs.

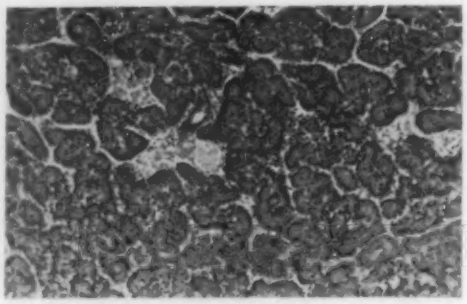


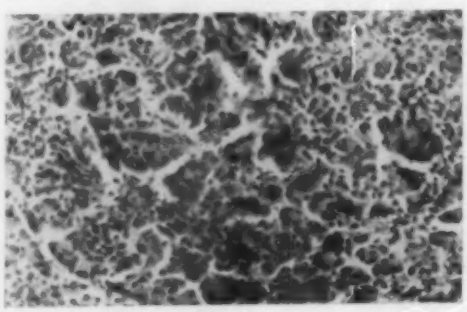
Fig. 1.—Pancreas of normal 5-day-old dog. Hematoxylin and eosin stain; reduced ⅓ from mag. × 150.

In the pancreas of the majority of the puppies born dead, namely, in 10 of the 13 from the carbon tetrachloride group and in 5 of the 8 stillborn puppies from the dietary group, disappearance of perinuclear basophilia, very marked eosinophilia and association of the parenchyma, loss of normal organization of acini, and focal necroses were present. The same changes were displayed by the puppies dead within 20 days. The lungs were normal in all these animals (Table 3 and Figs. 2 to 8).

TABLE 3.—*Pancreatic Changes in Experimental Groups*

Experiment	No. Puppies Born Dead	Pancreatic Changes		
		Eosinophilia	Dissociation	Necroses
CCl_4	13	2	1	7
Dietary	8	2	1	3

Fig. 2.—Stillborn puppy of dog on deficient diet. Pancreas. Center, normal parenchyma. Right and left, dissociated parenchyma. Hematoxylin and eosin stain; reduced ⅓ from mag. × 250.



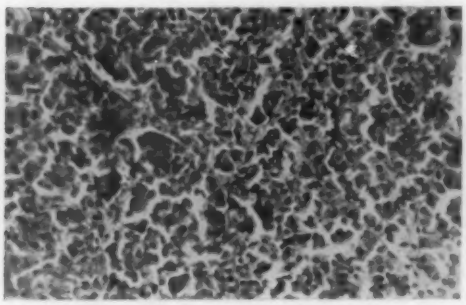


Fig. 3.—Six-day-old puppy born of dog on deficient diet. Dissociation of the pancreatic parenchyma. Hematoxylin and eosin stain; reduced ⅓ from mag. × 250.

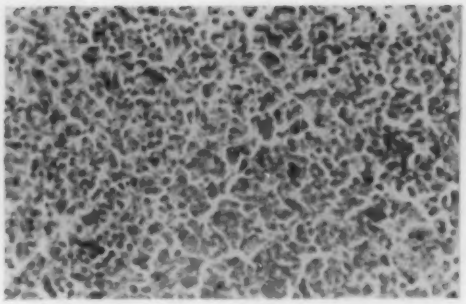


Fig. 6.—Four-day-old puppy born of dog on deficient diet. At botttom of picture, necrosis of pancreatic parenchyma. Hematoxylin and eosin stain; reduced ⅓ from mag. ×200.

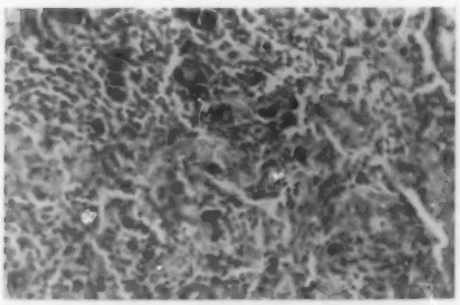


Fig. 4.—Stillborn puppy of dog treated with carbon tetrachloride. Pancreas, dissociation of parenchyma. Normal structure of acini has disappeared. Hematoxylin and eosin stain; reduced ⅓ from mag. × 250.

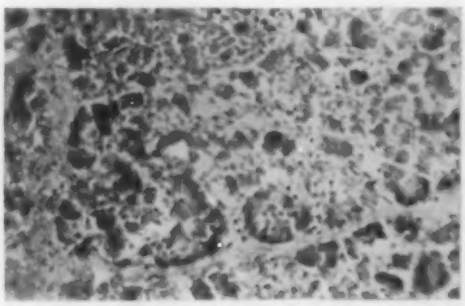
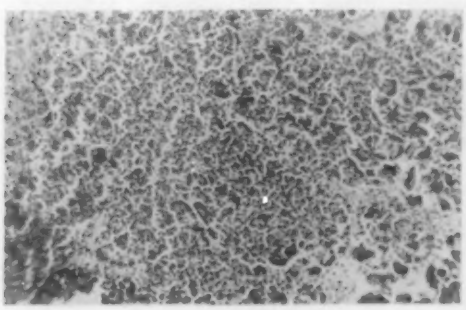
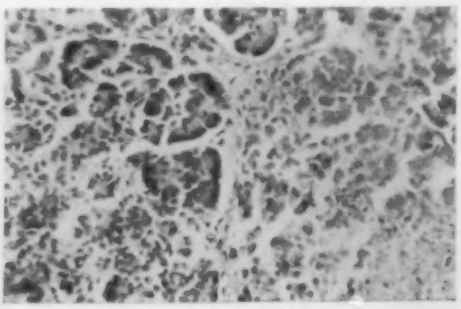


Fig. 7.—One-day-old puppy born of dog treated with carbon tetrachloride. Pancreas. Extensive grave necrosis. Hematoxylin and eosin stain; reduced ⅓ from mag. × 150.

Fig. 5.—Ten-day-old puppy born of dog treated with carbon tetrachloride. Dissociation of pancreatic parenchyma. Hematoxylin and eosin stain; reduced ⅓ from mag. × 100.

Fig. 8.—Thirty-two-day-old puppy born of dog treated with carbon tetrachloride. Pancreas. At left, normal parenchyma. At right, extensive necrosis. Hematoxylin and eosin stain; reduced ⅓ from mag. × 300.





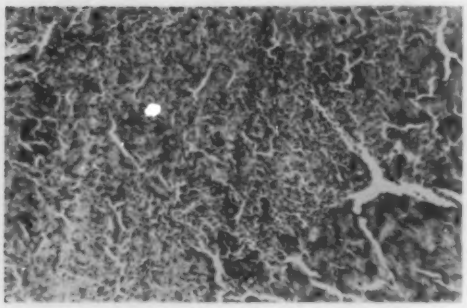


Fig. 9.—Eighteen-day-old puppy born of dog on deficient diet. Fibrosis of the pancreas. Hematoxylin and eosin stain; reduced ⅕ from mag. × 150.

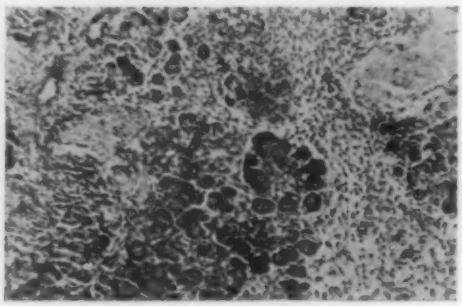


Fig. 12.—Thirty-three-day-old puppy born of dog treated with carbon tetrachloride. Fibrosis of the pancreas. Hematoxylin and eosin stain; reduced ⅕ from mag. × 150.

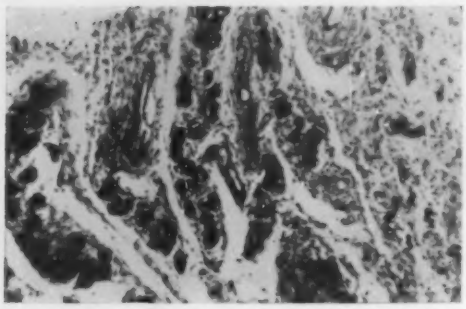


Fig. 10.—Twenty-day-old puppy born of dog on deficiency diet. Fibrosis of the pancreas. Mallory's stain; reduced ⅕ from mag. × 100.

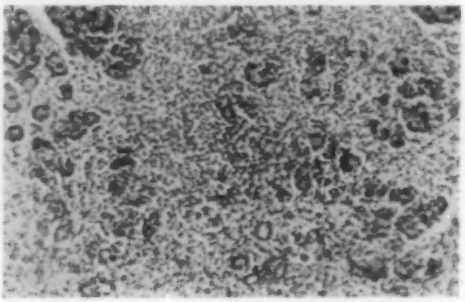


Fig. 13.—Eighty-three-day-old puppy born of dog treated with carbon tetrachloride. Grave fibrosis of the pancreas. Parenchyma invaded with connective tissue, few acini visible. Hematoxylin and eosin stain; reduced ⅕ from mag. × 150.

Fig. 11.—Thirty-one-day-old puppy born of dog on deficiency diet. Fibrosis of the pancreas. Hematoxylin and eosin stain; reduced ⅕ from mag. × 150.

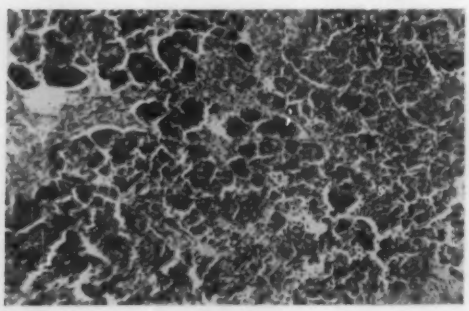
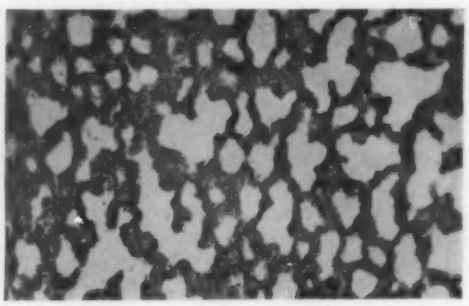


Fig. 14.—Lung of normal 15-day-old puppy. Hematoxylin and eosin stain; reduced ⅕ from mag. × 150.



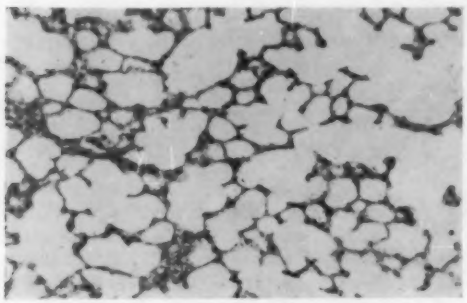


Fig. 15.—Thirty-one-day-old puppy born of dog on deficient diet. Pulmonary emphysema. Hematoxylin and eosin stain; reduced ⅙ from mag. × 150.

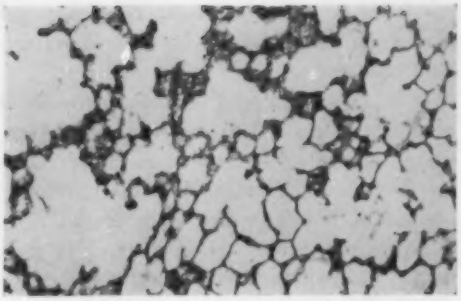


Fig. 16.—Eighty-three-day-old puppy born of dog treated with carbon tetrachloride. Hematoxylin and eosin stain; reduced ⅙ from mag. × 150.

In the puppies living beyond 18 days, more advanced stages of the pancreatic change were found—more or less extensive fibrosis, which was present in all the eight animals (Table 4 and Figs. 9 to 13). In addition, their lungs were not normal either, emphysema (Table 4 and Figs. 14 and 15) with some dilated bronchi characterizing every one of them.

TABLE 4.—*Pancreatic and Pulmonary Changes in Puppies Alive After Eighteen Days*

Experiment	Total No.	Pancreatic Fibrosis	Pulmonary Changes
CCl_4	8	8	8
Dietary	3	3	3
Control	20 (4 killed)	..	..

COMMENT

It became evident from the experiments that in the last stage of pregnancy a relatively mild toxic injury or a deficient diet, both too mild to bring about changes in the mother animal, is capable of inducing in the offspring a pancreatic lesion rapidly leading to death.

From among the pancreatic changes observed, disappearance of perinuclear basophilia, resulting in over-all eosinophilia, is, according to our previous experience a preliminary to cystic degeneration and, accordingly, to subsequent fibrosis. The fibrosis displayed by the present experimental series may be looked upon as the sequel to either the dissociation of the parenchyma or its necrosis. The appearance of focal necroses in the pancreatic parenchyma may be due to all kinds of toxic effect, as observed in previous experiments in consequence of poisoning with S. paradysenteriae toxin, tetrachloroethylene, or increased doses of carbon tetrachloride.

The daily amount of 1 ml. of carbon tetrachloride administered in the present series is not sufficient to bring about pancreatic changes in the adult dog, as has been subsequently proved by histology. It seems, however, that during intrauterine life the pancreatic parenchyma is so sensitive to effects of this kind that changes develop in it on the action of a very small amount of the toxic substance, the fraction of 1 ml. falling on one fetus.

The changes exhibited by the pancreas of the puppies were, in all probability, due to the intrauterine lesion, since after birth neither they nor their mothers were exposed to injury of any kind. The intrauterine injury, however, only started the change. The development of the lesion was still proceeding at the time when, and in spite of the fact that, the animal was not any longer exposed to injury. This was clearly shown by the fact that the gravity of the change increased parallel with the age of the puppy. It could perhaps, with due care, even be assumed that in those stillborn puppies in which no pancreatic change was found, the lesion was actually present but not yet discernible with the methods employed, since among the animals

surviving a certain time there was not a single one which did not have the characteristic change.

It would be tempting to evaluate the above results with respect to the etiology of fibrocystic disease. While the lesion observed is far from being identical with the one found in infants, it is also true that, according to our previous studies, such changes as were displayed by the present experimental series always develop into a picture closely resembling the morphological appearance of fibrocystic disease. The parallelism is still further supported by the regular appearance in both conditions of the pulmonary change consisting of emphysema with bronchial dilatation.

Still, the only conclusion we intend to draw from the experimental results is that without injury to the mother animal it is possible to induce pancreatic lesions in the offspring and that pulmonary changes are associated with these lesions. Further experiments will have to decide what role these and other intrauterine noxious factors play in perinatal mortality on the one hand and in the etiology and development of infantile fibrocystic disease of the pancreas on the other.

SUMMARY

A group of pregnant dogs was treated with carbon tetrachloride, and another group was fed on a methionine-free glue diet. About half of the offspring were delivered dead. The majority of the puppies born alive died within 20 days. After five weeks only two were living. The puppies surviving 20 days developed diarrhea characteristic of pancreatic failure.

In the mother animals no pathological changes whatever were found. The puppies exhibited mild pancreatic lesion at birth. With time, the lesion became increasingly grave, and pulmonary emphysema with bronchial dilatation also developed in the animals.

On the basis of the findings, the problem arises as to what role intrauterine noxious factors play in perinatal mortality and in the etiology of infantile fibrocystic disease of the pancreas.

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Studies in Sickle-Cell Anemia

V. Sickle-Cell Hemoglobin C Disease
(Report of Two Cases in Siblings with Clinical and Genetic Observations and a Brief Review of the Literature)

ROLAND B. SCOTT, M.D.
and
MELVIN E. JENKINS, M.D., Washington, D. C.

INTRODUCTION

Within the past few years, the application of newer knowledge, chiefly involving genetic, biochemical, and electrophoretic techniques, has resulted in the recognition of previously unknown intrinsic properties of human hemoglobin. The application of these newer tools to the study of sickle-cell anemia has revealed that the condition is not a simple disease entity but is in reality a hemolytic syndrome which may be separated into specific subtypes depending upon the variety of abnormal hemoglobin present.

To date, the hemoglobins which have been identified by chemical and/or electrophoretic studies are as follows *:

A—Normal adult hemoglobin
F—Fetal hemoglobin
S—Sickle-cell hemoglobin
C—C hemoglobin
D—D hemoglobin
E—E hemoglobin
G—G hemoglobin †

The pathologic effects of various known combinations of abnormal hemoglobins are listed in Table 1. The current designation of sickle-cell anemia is reserved for the type in which the genes responsible for sickling are homozygous. Statistically, this is the commonest variety. The second most frequently encountered type of sickle-cell disease in American Negroes is apparently sickle-cell-hemoglobin-C disease and is due to the simultaneous presence in the person of the sickle-cell gene and the gene responsible for C hemoglobin.[5] In a previous report [6] from this clinic, we described a child with sickle-cell-thalassemia disease. This is apparently the third most common type observed in the American Negro and is due to the simultaneous presence of the sickle-cell gene and the thalassemia gene. This latter variety probably accounts for the majority of cases of sickle-cell disease which have been reported in the American literature involving white persons of Mediterranean ancestry.‡ The other possible clinical types included in Table 1 are rare at present.

Sickle-cell-hemoglobin-C disease is the subject of this report. Although this type has emerged as a fairly characteristic clinical entity, there is a dearth of its description in the pediatric literature. In order to bring this particular variety of sickle-cell disease to the attention of a larger number of physicians caring for children, we wish to report studies on two siblings with the condition and to review briefly the current literature on the subject.

REPORT OF CASES

CASE 1.—R. C., a 12-year-old Negro boy, was referred to our service on May 12, 1954, from another hospital for evaluation of continuous pains in the back, abdomen, and flanks of one day's duration. This patient had been followed at the referring hos-

Submitted for publication Sept. 18, 1954.

From the Department of Pediatrics of Howard University College of Medicine and the Pediatric Service of Freedmen's Hospital.

* References 1-4.

† Since the preparation of this manuscript, a new hemoglobin (Hemoglobin H) has been reported (Rigas, D. A.; Koler, R. D., and Osgood, E. A.: New Hemoglobin Possessing a Higher Electrophoretic Mobility Than Normal Adult Hemoglobin, Science **121**:372 (March 11) 1955).

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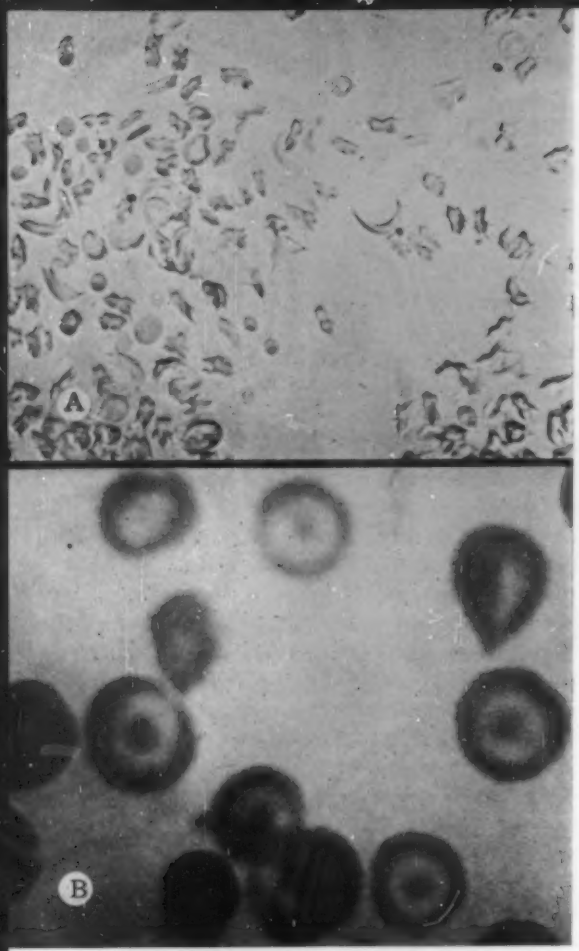

Fig. 1.—*A*, moist preparation (reduced approximately ¼ from mag. × 700) using sodium metabisulfite method demonstrating approximately 75% sickling of all erythrocytes, and *B*, a segment of the peripheral blood smear (reduced approximately ¼ from mag. × 2017) showing target cells in Case 1.

pital since the age of 2 months at both regular and irregular intervals. His first admission to the outpatient service was for a diarrhea which responded in three days followed by a short recurrence one month later. Blood cell counts at these times revealed only a mild anemia.

His first hospitalization was at the age of 5 years for abdominal pain, the cause of which was not elicited. However, during the same year a second hospitalization was required for abdominal and leg pains, during which time one blood smear revealed 80% sickling in 24 hours, which resulted in a diagnosis of sickle-cell anemia despite a hemoglobin of 11 gm. per 100 cc.

There were two further admissions—one at 8 years of age for abdominal pain and swelling of the right sternoclavicular joint, and the other, in 1950, was required for "arthritis" of the right elbow. An x-ray revealed demineralization of the metaphysis of proximal portions of both ulna and radius.

At no time during the above admissions and numerous clinic visits were the physical findings or laboratory data striking. The spleen was palpable on only one occasion, at 8 years of age. Icterus was never observed clinically. The hemograms were never remarkable in 50 examinations which averaged 3,700,000 RBC and 10.6 gm. of hemoglobin per 100 cc. In only 10 of the 50 determinations were the hemoglobin values below 10 gm. per 100 cc., and none of these were below 9 gm.

At the time of his admission to this institution, his general appearance was that of an acutely ill child who was weak and perspiring freely. The scleras were yellow. He complained rather violently of pains in the abdomen, back, and side.

The lung fields were clear. A Grade I systolic murmur at the cardiac apex was elicited. The splenic tip, which was barely palpable, was firm. There was some resistance to flexion of the neck and back but no definite abnormal neurological signs.

Laboratory Data.—Red blood cell count 5,570,000, hemoglobin 13.6 gm. per 100 cc. However,

TABLE 1.—*Effects of Some Known Combinations of Abnormal Hemoglobins*

	Common Nomenclature	Hemoglobin * Combination	Clinical Features
1.	Sickle-cell trait	A, S	Asymptomatic, sickling in reducing medium, no anemia
2.	Sickle-cell anemia	S, F	Severe anemic crises, sickling on direct smear
3.	Hemoglobin C trait	A, C	Asymptomatic, target cells, no sickling or anemia
4.	Hemoglobin C disease (homozygous)	C	Mild anemia, mild pain, target cells
5.	Sickle-cell-hemoglobin-C disease	S, C	Mild anemia, splenomegaly, pains, target cells, sickling of red cells
6.	Hemoglobin-C-thalassemia disease	A, C	Anemia, hypochromia, target cells, no sickling
7.	Hemoglobin D trait	A, D	Asymptomatic, no sickling
8.	Sickle-cell-hemoglobin-D disease	S, D	Anemia, sickling in reducing medium
9.	Hemoglobin E trait	A, E	Asymptomatic, no sickling
10.	Hemoglobin-E-thalessemia disease	E, F, A	Clinical and hematologic signs of Mediterranean anemia, no sickling
11.	Sickle-cell-thalassemia disease	S, F, A	Moderate to severe anemic crises, sickling on direct smear, target cells
12.	Thalassemia minor (Cooley's trait)	A, F	Asymptomatic or mild anemia
13.	Thalassemia major (Cooley's disease)	F, A	Severe hemolytic crises

* Variable amounts of F hemoglobin are found in many of these conditions, particularly those characterized by anemia.

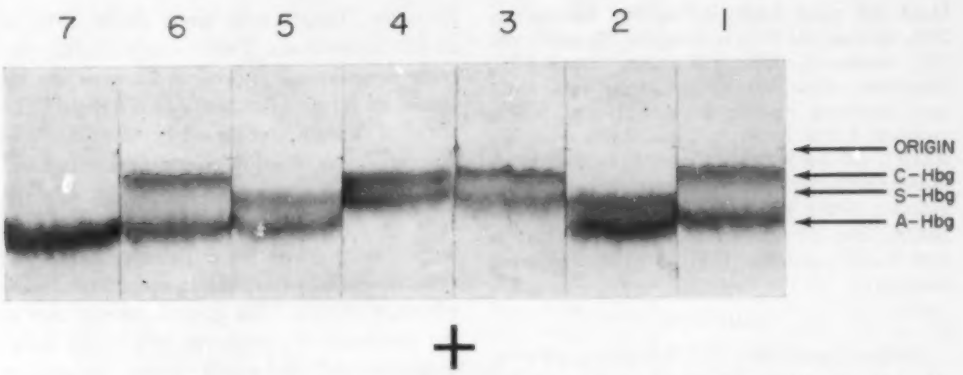

Fig. 2.—Classification of hemoglobin according to filter paper electrophoretic analysis of patients and family: 1. father—A,C hemoglobins (hemoglobin C trait); 2. mother—A,S hemoglobins (sickle-cell trait); 3. patient—C,S hemoglobins (sickle-cell-hemoglobin-C disease); 4. patient—C,S hemoglobins (sickle-cell-hemoglobin-C disease); 5. sibling—A,S hemoglobins (sickle-cell trait); 6. paternal uncle—A,C hemoglobins (hemoglobin C trait); 7. paternal uncle—A hemoglobin (normal adult).

total hemoglobin mass based on blood volume determinations was only 341 gm., which was about 20% below the expected value. White blood cell count 12,400, with 69% P. M. N., 29% lymphocytes, 2% monocytes, hematocrit 38%. Sickling test (sodium metabisulfite method) revealed 75% sickling in 15 minutes (Fig. 1*A*). Reticulocyte count 0.4%, osmotic fragility was decreased (initial 0.39%, complete 0.21%; control: initial 0.42%, complete 0.36%). Alkali denaturation revealed 1.2% resistant hemoglobin.

Urinalysis was negative except for a low specific gravity of 1.014. Vasopressin injection (Pitressin) urinary concentration test showed an inability to concentrate above 1.014.

Chemistry.—N. P. N. 24 mg. per 100 cc., glucose 112 mg. per 100 cc., CO_2 25 mEq. per liter, chlorides 104 mEq. per liter, total protein 9.29 gm. per 100 cc., cholesterol 175 mg. per 100 cc., with esters of 48% (84 mg.), alkaline phosphatase 5.05 Bodansky units. Icterus index was 12.45 units with indirect Vandenberg of 1.27. Total bilirubin 2.25 mg. Cephalin flocculation was 3+ at 24 hours, 4+ at 48 hours.

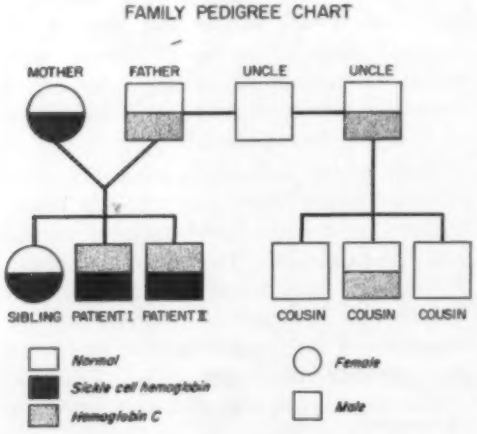

Fig. 3.—The family genetic pattern of hemoglobin type as revealed by paper electrophoresis.

Stained blood smear revealed over 50% target cells (Fig. 1*B*). Paper electrophoretic analysis resulted in migrations of hemoglobins of both S and C types (Fig. 2). Family genetic pattern is shown in Figure 3 as revealed by paper electrophoresis.

Bone marrow slides were diffusely hypercellular with many clumps. Erythrogenesis was increased and normoblastic. Granulopoiesis was relatively decreased E:G ratio = 1: 1.8). X-rays of entire skeleton including the wrist, ribs, spine, and pelvic bones showed slight demineralization associated with coarsening of the trabecular pattern consistent with early changes seen in a hemolytic anemia.

This child responded dramatically to infusions and bed rest in 48 hours.

Case 2.—M. C., a 9-year-old boy, sibling of Case 1, was seen in the outpatient department of another hospital at the age of 2 years for recurrent pain around the umbilicus. Hemoglobin was 10.5 gm. per 100 cc. at that time, with a red cell count of 3,300,000. Ninety-four per cent of the red cells sickled in 24 hours. He has had vague pains since 2 years of age, with only one attack of moderately severe pain in the antecubital area, at 9 years. There have been no hospitalizations. Average red cell count was 3,800,000 in 33 determinations. Hemoglobin averaged 10.4 gm. per 100 cc. in 36 determinations.

Present study reveals red blood cell count of 3,960,000, hemoglobin 10.5 gm. per 100 cc., white

blood cell count 8,600; differential: lymphocytes 70%, neutrophiles 26%, eosinophiles 2%, monocytes 2%, hematocrit 30%, reticulocyte count 1.2%. Peripheral smear revealed 32% target cells. There was decreased osmotic fragility (initial 0.39%, complete 0.21%; control: initial 0.42%, complete 0.33%), sickling 95% in 15 minutes (sodium metabisulfite method). Bone marrow was diffusely hypercellular; x-rays of long bones were negative. This patient, like his brother, showed hemoglobins of both S and C varieties (Fig. 2) on electrophoretic analysis.

COMMENT

Under conditions of filter paper electrophoresis at pH 8.6, normal adult hemoglobin (Type A) has the fastest mobility. In the order of decreasing relative speed the abnormal hemoglobins are F, G, S and D, C and E.§ Although S and D hemoglobins have the same mobility, the latter can be identified by its greater solubility in the reduced state and its inability to cause sickling of erythrocytes.‖ Likewise, hemoglobins C and E have practically identical mobility at pH 8.6, however, they have different chemical solubilities.¶ and the C variety is associated with the presence of target cells. Hemoglobin F can be most readily identified by its increased resistance to alkali denaturation,[10] however, electrophoretic [11] and serologic # identification techniques have also been reported.

The pathologic effects of the various known combinations of abnormal hemoglobins are listed in Table 1. The two cases reported here conform closely to the genetic, clinical, and hematologic picture presented by previously described cases * (Tables 2 and 3, Fig. 2).

With few exceptions, all of the reported patients had mild clinical and hematologic courses. Spleens were enlarged in 16 of the 19 cases. Target cells were above 30% in all but three cases. There was a slightly decreased osmotic fragility, and almost no increase in serum bilirubin was observed. The survival time of transfused erythrocytes was markedly shortened in two patients studied.[5]

A review of the literature reveals that the ages of the reported cases are somewhat higher than usual for a primary hemolytic syndrome. Only four of the cases were below 10 years of age. This is undoubtedly due to the mildness of symptoms which will delay diagnosis and also to the recent recognition of this disease.

The family reported here is quite interesting in that all members show some hemoglobin abnormality, with two of the three children having sickle-cell-hemoglobin-C disease. The mother carries the sickle-cell trait and the father carries the trait of C hemoglobin (Fig. 3).

One paternal uncle shows C trait, as does one of his three sons, whose tracings are not shown. The patients both had symptoms fairly early but have experienced a very mild course with only three hospitalizations for Patient 1 and none for Patient 2.

Awareness of this new hemolytic syndrome is necessary in order to avoid confusion with similar entities (Table 4). Patient 1 was thought to have the usual type of sickle-cell anemia from the ages of 5 to 12 years. Patient 2 had been considered a sickle-cell trait case. It may well be that some of the reported cases of sickle-cell disease with serious complications in the absence of anemia in retrospect represent combinations of S and C hemoglobins.†

Some of the thalassemia-minor-like cases observed in the Negro may represent hemoglobin C trait states (combination of normal and C hemoglobins). The benign hemoglobin C trait has been found to occur in about 2% to 3% of American Negroes, and the blood smear may appear normal except for the presence of target cells.‡ Likewise, homozygous hemoglobin-C disease may simu-

§ Itano, H. A.: Personal communication to the authors.

‖ Itano, H. A.: Personal communication to the authors.

¶ Itano, H. A.: Personal communication to the authors.

References 12 and 13.

* References 5 and 14-16.

† References 17-20.

‡ References 15 and 21.

TABLE 2.—*Summary of Findings in Other Reported Cases (Sickle-Cell-Hemoglobin-C Disease)*

Author	Age, Yr.	Sex	Crises	Spleen	RBC/Cc.	Hgb., Gm./ 100 Cc.	Ret., per Cent	Per Cent Target Cells	Fragility (Osmotic), per Cent	Serum Bilirubin, Mg./ 100 Cc.	Alkali Denaturation, per Cent
1. Ranney and co-workers	15	M	Frequent arthritis	Not palpable	3,800,000	11-12	3	20-40	.....	0.9	...
2. Ranney and co-workers	24	M	One	5 cm.	3,900,000	10-13	4	30-40	.....	...	...
3. Ranney and co-workers	27	F	Frequent joint pain	3 cm.	.....	10-12	3-6	30-40	0.32-0.28	...	...
4. Ranney and co-workers	13	F	One	Barely palpable	.....	8-11	4	4	.....	...	...
5. Ranney and co-workers	13	M	None	4 cm.	.....	10-12	2.4	10	0.42-0.22	...	...
6. E. Kaplan and co-workers	12	F	None	6 cm.	4,300,000-5,300,000	10-12	1.2-2.8	80	0.45-0.18	...	...
7. E. Kaplan and co-workers	10	M	Hemolytic	3 cm.	3,700,000-4,300,000	9-11	1-4	70	0.37-0.18	0.5	...
8. E. Kaplan and co-workers	4	F	Anemic	2 cm.	3,200,000-3,800,000	8-10	3.5-6	45	0.42-0.18	0.4-0.6	...
9. J. V. Neel and co-workers	8	M	Pain	Enlarged	2,400,000-4,400,000	7.0-9.6	4.6-6	60	.....	...	...
10. J. V. Neel and co-workers	10	F	Pain	Enlarged	3,100,000-4,500,000	7.2-11	0.6-7.5	60	0.37-0.21	0.3-1.3	...
11. J. V. Neel and co-workers	5	M	Pain	Enlarged	3,100,000-4,800,000	8.0-10.8	0.7-5	62	.....	0.1-0.3	...
12. J. V. Neel and co-workers	6	F	Pain	Enlarged	2,500,000-4,300,000	9.3-10	2.8	84	0.37-0.18	...	...
13. Smith and Conley	35	M	Hematuria	Enlarged	3,200,000	11.2	...	+50	.....	2.3	3.8
14. Smith and Conley	16	F	Leg pain; hematuria	Palpable	.....	12	...	Preponderant	.....	...	6.0
15. Smith and Conley	20	F	Anemic	Palpable	.....	Hct.* = 23	...	Preponderant	.....	...	4.8
16. Smith and Conley	15	F	Leg pain; anemic	Not palpable	.....	.....	...	Preponderant	.....	...	4.5
17. Smith and Conley	13	M	Asymptomatic	Palpable	.....	Hct. = 39	...	Preponderant	.....	...	5.0
18. Smith and Conley	15	F	Pain	Palpable	4,190,000	.....	...	Preponderant	.....	4.6	2.0
19. Smith and Conley	18	M	Joint pain	Not palpable	.....	Hct. = 35	...	Numerous	.....	1.5	−2.0

* Hematocrit.

TABLE 3.—*Laboratory Findings in Our Cases*

Member	Age, Yr.	Hgb. C	Hgb. S	Hgb., Gm.	Reticu., per Cent	Sickling, per Cent	Target Cells, per Cent	Osmotic Fragility, per Cent	Alkali Denaturation, per Cent	Serum Bilirubin, Mg.
R. C.—Patient 1	12	+	+	9.0-13.8	0.4	30	25	0.39-0.33	1.2	2.2
M. C.—Patient 2	9	+	+	8.5-13.2	1.4	40	32	0.39-0.21	3.2	0.72
V. C.—Sibling	11	—	+	12	0.5	95	0	0.42-0.33	1.2	...
Mrs. M. C., Mother	36	—	+	10.4	0.4	45	0	0.48-0.30	0.2	...
Mr. C. C., Father	41	+	—	13.6	0.4	0	20	0.42-0.33	0.9	...
B. C., Paternal uncle	..	..	..	11.2	...	0	0	.....	...	...
A. C., Paternal uncle	49	+	—	11.8	...	0	20	.....	...	...
Cousin *	11	+	—	14.3	...	0	0	.....	...	...
Cousin *	13	—	—	13.6	...	0	0	.....	...	...
Cousin *	9	—	—	18.2	...	0	0	.....	...	...

* Sons of A. C.

TABLE 4.—*Differential Diagnoses of the Common Sickling Diseases*

Finding	Sickling Trait	Sickle-Cell Anemia (Homozygous)	Sickle-Cell-Hemoglobin-C Disease
Anemia	Absent	Moderate to severe	Mild or absent
Jaundice	Absent	Often present	Absent to mild
Pains (crises)	Absent	Frequent, severe	Present, less severe, less frequent
Spleen	Normal	Enlarged (early)	Enlarged as a rule
Sickling of RBC	Absent	Present both on dry film and wet prep.	Usually absent on dry but present on wet prep.
Target cells	Usually absent	Present	Numerous
Reticulocytosis	Absent	Present	Minimal
Serum bilirubin	Normal	Elevated	Normal or slightly elevated
Bone marrow	Normal	Erythroid hyperplasia (marked)	Erythroid hyperplasia (moderate)
Survival time of transfused erythrocytes	Normal	Decreased	Decreased
Heart	Normal	Often enlarged	Rarely enlarged
Fecal urobilinogen	Normal	Increased	Increased
Parents	S gene in one	S gene in both	S gene in one C gene in other *
Resistance of RBC to hypotonic saline	Normal	Increased	Increased
Electrophoresis	S hemoglobin; normal hemoglobin	S hemoglobin	S hemoglobin C hemoglobin
Fetal or alkali-resistant hemoglobin	Normal value	Elevated	May be slightly elevated
Growth and nutrition	Normal	Usually impaired	Approaches normal
Clinical course	Normal	Frequent crises	Symptoms mild as a rule
Treatment (blood transfusions)	None needed	May be necessary	Rarely if ever necessary

* C gene trait may be identified in the asymptomatic carrier state by (1) absence of sickling, (2) high incidence of target cells, (3) increased resistance to hypotonic saline, and most precisely by (4) presence of abnormal hemoglobin demonstrated by electrophoresis.

late thalassemia states.§ Sickling of erythrocytes is absent in homozygous hemoglobin-C disease,‖ as well as in combinations of C with normal or thalassemia trait hemoglobin.¶

A review of the reported cases of sickle-cell-hemoglobin-C disease reveals a fairly characteristic clinical picture, namely, relatively mild crises, erythrocyte sickling, high incidence of target cells on blood smears associated with an enlarged spleen. A definitive diagnosis can be made readily by the use of filter-paper electrophoresis. The prognosis is variable as to clinical course, but in general this disease is milder than the commoner variety (homozygous S) of sickle-cell anemia.

It is interesting that Smith and Conley [15] are impressed with the severity of the disease picture in some of the patients with sickle-cell-hemoglobin-C disease. These persons can become profoundly anemic during a sudden hemolytic episode, such as that which occurred in two of the patients during pregnancy. Leg and abdominal pain appear much less frequently. However, it is noteworthy that two patients had episodes of unilateral

§ References 16, 22, and 23.

‖ References 15, 22, and 23.

¶ References 24 and 25.

gross hematuria and one exhibited recurrent convulsive episodes.

SUMMARY

A study of two patients with sickle-cell-hemoglobin-C disease is presented. The clinical picture of mild hemolytic anemia, infrequent pains, enlarged spleen, and numerous target cells on peripheral smear in a Negro patient whose blood exhibits the sickling phenomenon should immediately suggest the possibility of sickle-cell-hemoglobin-C disease. The diagnosis can easily be confirmed by paper electrophoresis.

The disease is inherited in the same manner as the commoner homozygous sickle-cell disease, with one parent contributing the sickling trait, the other the trait of hemoglobin C. A complete genetic evaluation of the family hemoglobin distributions is essential for full insight into any individual case and provides an opportunity for discovery of unsuspected cases.

In general, this subtype is milder in clinical symptomatology than the commoner variety (homozygous S); however, cases of exceptional severity have been reported. Awareness of this new hemolytic syndrome is necessary in order to avoid confusion with other hemolytic anemias which may produce a similar clinical picture. The differential diagnosis is discussed. Treatment is symptomatic, and blood transfusions are rarely necessary.

Dr. William Bullock, Chief Hematologist, Freedmen's Hospital, and Dr. Elizabeth Smith, Department of Pharmacology, Walter Reed General Hospital, Washington, D. C., supplied the paper electrophoresis analyses. Dr. H. A. Itano gave suggestions in the preparation of the manuscript. Dr. Frank Johnson assisted with the photographic illustrations. Mr. James Ross, Medical Technician, assisted with hematological studies.

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News and Comment

ANNOUNCEMENTS

Coming Examinations to Be Held by The American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold oral examinations according to the following schedule:

Chicago—Oct. 7, 8, and 9, 1955
Washington, D. C.—Dec. 2, 3, and 4, 1955

Postgraduate Course in Tuberculosis of Childhood.—The Department of Pediatrics of New York University College of Medicine is offering a course in tuberculosis for pediatricians and general practitioners. This will be given by the Chest Clinic of the Children's Medical Service of Bellevue Hospital, on Sept. 26-30, 1955.

This course is designed for pediatricians or general practitioners interested in tuberculosis in infants and children. It will comprise lectures, clinical demonstrations, and discussions of the diagnosis, prognosis, and treatment of tuberculosis and other pulmonary disorders. Tuition is $60.

Those interested should apply to Edith M. Lincoln, M.D., Bellevue Hospital, New York 16.

PERSONAL

Appointment for Dr. B. M. Kagan.—Dr. B. M. Kagan, formerly Professor of Pediatrics at the Northwestern University Medical School, Chairman of the Department of Pediatrics and Director of the Department of Pediatric Research at the Michael Reese Hospital, has been appointed Director of the Department of Pediatrics at the Cedars of Lebanon Hospital in Los Angeles. He will begin his new duties on Sept. 1, 1955.

Mongolism in Twins

Its Bearing upon the Question of the Etiology of Mongolism

ABRAHAM FRIEDMAN, M.D., Haifa, Israel

Of the various aspects of Mongolism none is more intriguing than the problem of its etiology, and among the methods of investigation which contributed to the elucidation of this problem is the study of twins in which one or both are Mongoloid. Considering the comparatively high incidence of Mongolism generally, which is about 1 to 2 in every 1000 births,[1] it is rather surprising to note that cases of Mongolism in twins are very rare. Moreover, the first cases to be reported in the literature were done so merely as medical curiosities, without realization of the bearing that they may have upon the question of etiology. They were, therefore, reported not only infrequently but also inadequately. It was as late as 1923 that Halbertsma [2] pointed out, for the first time, the value of such cases for the elucidation of certain aspects of the etiology of Mongolism.

Since then, the number of cases reported has been accumulating steadily. Thus, Benda [3] found more than 80 cases of Mongolism in twins recorded in the literature up to 1947, although he considered only 63 of these to be reliable. Warner,[4] in 1949, collected data from the literature on 101 sets of twins in which one (81 cases) or both (20 cases) were Mongoloid, and he added a case of his own. Gedda,[5] in 1951, studied a total of 121 sets of twins, collected from the literature, in which one (96 cases) or both (25 cases) were Mongoloid. Oster,[1] in 1953, found only 98 instances of Mongolism in one (79 cases) or both (19 cases) of twins reported in the literature, excluding a certain number of cases "where the diagnosis of mongolism is doubtful and where sex and/or zygosity are very uncertain." To these may be added the case of Cozzolino,[6] that was omitted by all, and the more recently reported cases of Dawson,[7] Cook [8] (two cases), Posteraro,[9] Robertson,[10] Engler [11] (three cases), Morris and MacGillivary [12] (two cases), Lang-Brown and co-workers [13] (four cases), and Young.[14] These bring the total number of cases reported up to the present time to 110, taking Oster's figure as basis.

This seemingly large number of cases would ordinarily be sufficient for accurate statistical analysis. One should, therefore, be in a position to draw, from the data at hand, valid conclusions as to the etiology of Mongolism. It is, however, the consensus of opinion of all students of the problem that the number of cases recorded in the literature is as yet inadequate for the purpose in point. This is due mainly to the fact that the zygosity diagnosis of many of the recorded cases is too uncertain, and, because of the difficulties inherent in its determination, one cannot be too sure of the accuracy of the zygosity diagnosis in some of the others.

There is, however, another limiting factor of great importance, namely, the possibility that the cases of Mongolism in twins recorded in the literature do not represent a random sample of all the cases of Mongoloid twins existing in the population. Certainly, all cases of Mongolism in twins do not stand an equal chance of being published in the literature. The more unusual type of case, such as monozygous twins or concordant twins, obviously, stands a greater

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chance of being reported than the commoner type of case, such as dizygous or discordant twins. It is, therefore, highly probable that significant statistical bias existed in the original reporting of cases, and this fact, certainly, limits the accuracy of any statistical analysis. It is true that the sex distribution of the 113 recorded cases (including those reported in this paper) is 42 of unlike-sexed pairs and 71 of like-sexed pairs, as compared with a theoretical expectancy, among the 113 pairs, of 37.7 for unlike-sexed and 75.3 for like-sexed pairs, namely, a ratio of 1 : 2. These figures give a χ^2 value of 0.736, which is not significant statistically and, therefore, represents evidence that the available cases in the literature may actually represent a valid random sample. Nevertheless, the possibility of a statistical bias in the original collection of cases still exists.

Recently, three cases of Mongolism in twins came to our attention within a short period of two months. One was a set of unlike sex in which the male was Mongoloid and the female was normal. The second was a set of like sex (males) one of whom was Mongoloid and the other was normal. The third was a set of unlike sex in which the male was Mongoloid and the female was normal. It is the purpose of this paper to record these three cases and to consider the bearing that the study of Mongolism in twins, generally, may have upon the question of the etiology of Mongolism.

REPORT OF CASES

CASE 1.—B. C. a 9-year-old Negro male Mongoloid, was seen, together with his normal co-twin sister, at the Dr. Julian D. Levinson Research Foundation, for the first time, on Sept. 3, 1954.

The family history was negative for any neuropsychiatric conditions, including Mongolism. There was a history of twins on both sides of the family. The mother was 37 and the father was 39 years old when the twins were born. The twins were the result of the second pregnancy, the first having terminated in a miscarriage. Following the twin pregnancy the mother miscarried three more times, the first of which was another set of twins.

The pregnancy of the twins was complicated by repeated uterine bleedings which occurred at each of the missed menstrual periods.

The twins were delivered on July 5, 1945, at the Cook County Hospital, after a four-hour labor. The first twin to be born was the Mongoloid boy, by a spontaneous cephalic delivery. His birth weight was 5 lb. 2 oz. (2325 gm.). He was cyanosed at birth, and his respiration and cry were delayed. He was given oxygen and was kept in an incubator for two weeks. The normal twin girl was born immediately after the Mongoloid, also by a cephalic delivery. Her birth weight was 4 lb. 2 oz. (1870 gm.). She breathed and cried spontaneously and did not require oxygen or incubator. There were two separate placentas.

The development of the female twin was entirely normal. She sat up at 6 months, walked at 10 months, and spoke words at 10 months and sentences at 16 months. The physical examination at the age of 9 years showed her to be normal physically and mentally. She was attending school and was in the fourth grade and doing well.

The Mongoloid twin developed slowly. He held his head up at nine months, sat at two years, and started walking at two and a half years. His first tooth came out when he was 3 years old. He spoke words at 3 and started making sentences at 7 years of age.

He had measles, German measles, and chickenpox without complications. At the age of 3 years he had a typical grand mal convulsion without fever but after a severe emotional excitement. He was susceptible to colds. He also had urinary incontinence during the day only, and the condition persisted to the time of the examination. The mother knew that the child had congenital heart disease, but she was never told that the child was Mongoloid. His vision was poor, and he had been wearing glasses since the age of 6 years. While sitting, he frequently and spontaneously assumed the Buddha position.

The physical examination of the patient, at 9 years of age, revealed a well-developed and well-nourished Negro boy who appeared severely mentally retarded. His hearing was good; his vision was fair, but his speech was poor, indistinct, and consisted mainly of single words. His skull was small, measuring 18 in. (45 cm.) in circumference, globular, and had a flattened occiput. His facial expression was typically Mongoloid. His eyes were slanting. There was no epicanthus and no strabismus, but there was a horizontal nystagmus. The ears were small and outstanding, and the ear lobules were very small and adherent. The lips were fissured. The teeth were irregularly aligned. The tongue was smooth and not projecting. The palate was high-arched and narrow. The heart was enlarged to percussion, and a loud, harsh Grade IV systolic murmur was heard at the second and third left interspaces. The extremities were flabby, hypotonic, and hyperextensible. The hands

were broad and flabby. The fingers were short and tapering. The little fingers were curved. There were no palmar horizontal lines. There were plantar furrows, and the gap between the first and second toe was wide.

Psychological evaluation showed an I. Q. of 41 on the Stanford-Binet scale. The blood cell count and the urine analysis were entirely normal. Phenylpyruvic acid test in the urine was negative. X-rays of the skull and chest were normal. X-rays of the hands and wrists showed a normal bone age, but there was shortening of the middle phalanx of the fifth finger bilaterally. The electroencephalogram showed multiple spike discharges, maximal in the occipital area.

Comment.—In this first case the problem of zygosity determination is a very simple matter, since the twins, being of unlike sex, must necessarily be dizygous.

CASE 2.—G. H., a 9-year-old Negro boy, was examined at the Dr. Julian D. Levinson Research Foundation on Sept. 17, 1954, for the first time.

The family history was negative for neuropsychiatric conditions. At the age of one month the child was given up by his mother to her cousin, who was the informant. A review of the birth charts in the hospital completed this information.

The mother was 24 years old at the child's birth. This was the mother's first pregnancy. It was complicated by a history of syphilis, a positive Wassermann test, and by a mild preeclamptic state. Subsequent to this pregnancy, the mother had one more pregnancy, resulting in a girl, who is now 8 years old and entirely normal.

The patient was born at the Cook County Hospital on Sept. 20, 1945. Labor was premature but spontaneous in onset and resulted in a twin delivery. The first of the twins was the patient, who was delivered by a normal spontaneous cephalic delivery after 10 hours of labor. His birth weight was 4 lb. 4½ oz. (1940 gm.). His Kahn test was negative. The patient remained in an incubator at the hospital for four weeks and was discharged at the age of 6 weeks.

The second twin was also a boy. He was delivered by a normal spontaneous cephalic delivery, five minutes after the first twin, and his birth weight was 3 lb. 10½ oz. (1650 gm.). This twin was in good condition, and his progress was satisfactory until the 28th day, when he developed a severe bloodly diarrhea; he died four days later.

A review of the birth records of the mother and twins revealed that the placenta and membranes were double. The family was not given a diagnosis of Mongolism in either of the twins. However, the records reveal that while a diagnosis of Mongolism was made in the first twin no such diagnosis is mentioned in the record of the second twin, who died. Furthermore, a review of the autopsy report of the second twin revealed no evidence whatsoever of the presence of Mongolism. The postmortem diagnoses were ulcerative colitis, duodenal ulcer, and prematurity, without any mention of Mongolism.

The patient's development was slow. He sat up at 9 months, crawled at 1½ years and walked at 2 years. He spoke words at 1½ years and sentences at 8 years of age.

The patient had measles, without complications. He was constantly constipated and had a chronic conjunctivitis. He, also, frequently and spontaneously assumed the Buddha position while sitting.

The physical examination of the patient revealed a well-developed and well-nourished Negro boy of 9 years whose facies was typically Mongoloid. His hearing and vision were good, but his speech was poor and very indistinct and consisted of single words only. His skull was small, measuring 19 in. (47.5 cm.) in circumference instead of 21 in. (52.5 cm.), globular, and had a flat occiput. The eyes showed slanting, marked conjunctivitis, left internal strabismus, and a mild epicanthus. The ears were small, and the lobule was small and adherent. The lips were fissured. The teeth were widely spaced and irregularly aligned. The lateral incisors were pointed. None of the permanent teeth had erupted as yet. The tongue was large, furrowed, and frequently protruding. The heart showed some enlargement and a Grade III systolic murmur at the base. The abdomen showed diastasis of the recti muscles. The extremities were flabby and hyperextensible, and during the examination the patient spontaneously assumed the Buddha position. The hands were short and broad. The little fingers were curved. There were no palmar horizontal lines and no plantar furrows.

Psychologic evaluation showed an I. Q. of 29 on the Merrill-Palmer scale. The blood count and urinalysis were normal. Phenylpyruvic acid test in the urine was negative. X-rays of the chest and skull were normal. X-rays of the wrists and hands showed a normal bone age and some shortening of the middle phalanx of the fifth finger. Kahn test was negative.

Comment.—In this second case the twins were of like sex. Their zygosity is, therefore, a matter of great importance to determine. Unfortunately, the early death of one of them made it impossible for any further study to be carried out. The only available criterion for assuming them to be dizygous is the presence of a double placenta and fetal membranes, as mentioned in the records.

CASE 3.—T. W. a 7-month-old white boy was seen at the Cook County Children's Hospital, were

he was admitted on Oct. 28, 1954, because of an upper respiratory infection.

The family history was negative for any neuropsychiatric conditions. The mother had twin sisters. The mother was 31 and the father was 35 years old when the twins were born. The mother had eight pregnancies, the seventh of which resulted in the twins reported here, and the eighth pregnancy terminated in a miscarriage. The first six pregnancies resulted in normal children who are all alive and well with the exception of the second child, who, at the age of one year, was operated upon for hydrocephalus and is doing well at present.

The pregnancy of the twins was entirely normal except for a pyelitis which cleared up with medication. The twins were born on March 7, 1954, at the Lewis Memorial Hospital, in Chicago. They were delivered spontaneously but prematurely in the eighth month of pregnancy after one and one-half hours of labor. The first twin to be born was the Mongoloid male, weighing 2 lb. 13 oz. (1275 gm.) at birth, and immediately afterwards the normal female was delivered, weighing 3 lb. 12 oz. (1700 gm.). Both were cephalic deliveries, and there were two placentas.

The neonatal period was uneventful. Both twins were kept in incubators in the hospital, the boy for two months and the girl for one month.

The development of the female twin was normal. She smiled at five weeks, held her head up at two months, rolled over at four months, sat up at six months, and stood up at seven and one-half months. When examined at the age of eight months she was found entirely normal physically and developmentally.

The development of the Mongoloid twin was very slow. He smiled at five months and was still not able to hold his head up when seen at eight months of age. He had frequent colds and was treated for diarrhea a month before his present admission to the hospital.

The physical examination revealed a poorly developed and poorly nourished white boy. His facies gave a Mongoloid impression. The skull measured 16½ in. (41.25 cm.) in circumference as compared with a chest measurement of 14 in. (35 cm.). The right occipital area was markedly flattened. The anterior fontanel was widely open. The eyes showed slanting and marked epicanthal folds. The ears were very small, slightly deformed, and had no lobules. The lips were fissured, and the palate was high-arched and narrow. The tongue was enlarged and protruded most of the time, the child sucking continuously on his protruding tongue. There were no teeth. The chest showed a very marked degree of pigeon-breast, with marked inspiratory retractions. The abdomen and genitalia were normal. The extremities were hypotonic, flabby, and hyperextensible. The hands showed no palmar horizontal lines and no curved little fingers. The feet showed bilateral plantar furrows and widened gaps between the big and second toes.

The work-up showed a mild anemia and a normal urine. The cerebrospinal fluid was clear; there were no cells, negative Pandy test, glucose 62 mg/100 cc., protein 22 mg/100 cc., chloride 109 mEq/liter, and culture sterile. Chest x-rays were normal. Skull x-rays revealed all the fontanels to be open. X-rays of the hand and wrist showed normal maturation of the ossification centers.

Comment.—As in Case 1, these twins are obviously dizygous, being of unlike sex.

GENERAL COMMENT

From the point of view of the elucidation of the etiology of Mongolism, the all-important problem in the study of twins, in which one or both are affected by Mongolism, is the correct determination of their zygosity. This is obviously a very simple matter where the twins are of unlike sex, since they are certainly dizygotic then. The problem is, however, entirely different when the twins are of like sex, since under such circumstances a knowledge of the methods of zygosity determination is essential for correct diagnosis. Unfortunately, many of the cases reported in the literature are inadequately studied from this point of view.

Of the various methods, available to the clinician, for the study of zygosity, not one is absolutely conclusive in every case. Thus, the morphologic similarities and dissimilarities between co-twins, although extremely important, may, nevertheless, be misleading. On the one hand, Mongolism occurring in one of a monzygous set of twins will cause such gross changes in that twin only that the twins will appear superficially dissimilar and may consequently be classified as dizygous. On the other hand, Mongolism occurring in both of a dizygous set of twins may produce such marked similar changes in both that they will appear superficially identical and will thus be classified as monozygous. The most important physical characteristics for the determination of zygosity are the color of the hair, eyebrows, and irises, as well as the skin color and texture. However, similarities between these

features are not conclusive for monozygosity, and even dissimilarities are not absolutely conclusive for dizygosity, although very suggestive.

An examination of the fetal membranes is one of the most useful methods of determining zygosity, and it is generally accepted that the presence of two separate and distinct placentas is strong evidence of dizygosity. It is known, however, that as high as 30% of monozygotic twins are born in dichorial placentas,[15] and a casual examination of the fetal membranes is, therefore, useless. According to Morrison,[16] the membranes must be properly examined grossly, as well as microscopically, in order to be of any value. Additional evidence for the zygosity of twins may be provided by a study of the placental blood vessels. Anastomosis between the blood vessels of the membranes indicates monozygosity, while a lack of anastomosis indicates dizygosity. But this too is apparently not absolute.

Of the more modern methods of zygosity determination in Mongolism, detailed blood-group studies are most helpful. This was first recommended by Orel[16] and was later expanded to include not only ABO and MN groups but also the complete Rh formula as well as any other blood factor. Any difference in the antigenic constitution of the blood types of the twins is, of course, conclusive evidence for dizygosity. The complete equality, however, of the two blood types can be considered as a very strong probability only, and not a mathematical certainty, for monozygosity.

A study of the dermatoglyphic patterns of the finger prints, as well as of the palm and sole prints, of the twins is also of great importance in the diagnosis of zygosity. As a criterion of twinning based on dermatoglyphic patterns, it is generally accepted that the difference between the two hands of either twin should be greater than the difference between the homolateral hands of the two twins.[17] This criterion of monozygosity has been found to hold true in the case of a set of concordant monozygous Mongoloid twins.[17] Dermatoglyphic patterns of Mongoloids show, however, certain trends of variation which characterize Mongoloids as a group.[18] Mongoloids differ from non-Mongoloids in their dermatoglyphics, not by the possession of morphologic characters peculiar to them but rather in the comparative frequencies of particular features. For example, whorls in fingerprint patterns of Mongoloids are less frequent than in non-Mongoloids.[19] Certain of these features have even been found helpful in the diagnosis of Mongolism.[20] This method, however, cannot as yet be considered conclusive in the diagnosis of zygosity of twins of which one or both are Mongoloid, although in the hands of the expert it can be of great service.

It is very desirable that every case of like-sex twins be thoroughly studied by all the above four methods of investigation. Then, only, can one hope to arrive at a correct diagnosis of zygosity with a reasonable degree of certainty. It is, however, very regrettable that in most cases in the literature this has not been done. Thus, of the 90 cases studied by Oster[1] 35 were of uncertain zygosity and only 63 had their zygosity determined with a variable degree of certainty.

The Table shows the relationship between zygosity and cordance of all known cases of Mongolism in one or both of twins. This Table is based on the case material collected from the literature by Oster,[1] with the addition of the cases of known zygosity and sex published since. These include the cases reported by Dawson,[7] Cook (two cases),[8] Posteraro,[9] Robertson,[10] Morris and MacGillivary (two cases),[12] Lang-Brown and co-workers (four cases),[13] Young,[14] and the three cases here recorded. There is a total of 113 cases, of which 21 were concordant, that is, both twins were Mongoloid, and 92 cases which were discordant, that is, only one twin was Mongoloid while the co-twin was normal. In 42 instances the twins were of unlike sex, that is, unmistakably dizygous, and all of these were discordant. Of the 71 instances of like-sex twins, 26 were probably dizygous, and all of these, with the exception of 3 cases, were also discordant,

Distribution of all Cases of Mongolism in Twins Reported in the Literature, According to Their Sex, Zygosity, and Cordance

Sex	Zygosity	Cordance	Cases No.	Total
Twin pairs of unlike sex	Certainly dizygous	Concordant *	0	42
		Discordant †	42	
Twin pairs of like sex	Probably dizygous	Concordant	3	26
		Discordant	23	
	Probably monozygous	Concordant	10	10
		Discordant	0	
	Uncertain zygosity	Concordant	8	35
		Discordant	27	
		Total	113	113

* Concordant means that both twins are Mongoloid.
† Discordant means that only one twin is Mongoloid.

while the 3 were concordant. Another 10 were probably monozygous, and all of these were concordant. The remaining 35 cases were of uncertain zygosity, and of these 8 were concordant and 27 were discordant.

On close examination of the Table a number of facts emerge which are fundamental to the study of the etiology of Mongolism. These facts are as follows: 1. Without exception, all sets of Mongoloid twins of unlike sex reported in the literature are discordant. Also, without exception, all concordant Mongoloid twins reported are of like sex. In other words, no set of twins of unlike sex which were both Mongoloid has ever been reported in the literature. 2. Without exception, all cases of discordant Mongoloid twins reported in the literature are dizygous. Also, without exception, all cases of monozygous twins reported in the literature are concordant. In other words, no set of monozygotic twins of which only one was Mongoloid has ever been recorded in the literature. 3. With the exception of three cases, all sets of concordant Mongoloid twins reported in the literature are monozygous.

From these basic facts certain conclusions can be drawn as to the validity of some of the many theories which to this day compete for the honor of providing an explanation of the etiology of Mongolism. From the point of view of twin studies, these many theories may be divided into two main groups: (*a*) the germ-cell theories, which assume the defect to be present in the gametes (maternal and/or paternal) before fertilization and (*b*) the environmental theories, which assume the defect to be produced after fertilization has taken place.

Among the germ-cell theories the principal ones are (*a*) the hereditary theory,[21] which assumes Mongolism to be due to the presence of one or more pathologic genes in the chromosomes, recessively or dominantly inherited; (*b*) the gametic mutation theory,[22] which assumes Mongolism to be due to the sudden spontaneous sporadic appearance of a pathologic gene in the chromosomes of the gametes; (*c*) the theory of defective ova,[23] which assumes Mongolism to be due to fertilization of ova which are of diminished viability and unsuitable to produce normal offspring.

Among the environmental theories the principal ones are (*a*) the nidation theory,[11] which puts the blame for the appearance of Mongolism on a pathologic state of the uterine mucosa (following curettage, recent pregnancy, advanced age, etc.); this results in poor nidation and, consequently, poor nutrition of the embryo and, therefore, inadequacy of development of many embryonic tissues; (*b*) the theory of maternal endocrine imbalance of Benda,[3] who believes that an endocrine imbalance of the mother, namely, hypopituitarism during the early months of pregnancy, is of decisive importance in the causation of Mongolism; (*c*) the theory of embryonic disease,[24] which postulates Mongolism to be due to any of a series of causative agents, including uterine hemorrhage, anoxia, intercurrent infections,

etc., operating at about the eighth week of fetal life.

The findings of the studies on twins in which one or both are Mongoloid can be of the greatest importance in the corroboration or invalidation of some of these theories. If, for example, without exception, all the monozygous twins recorded were found to be concordant and all the dizygous twins were found to be discordant, such a finding would speak very strongly in favor of one or the other of the germ-cell theories. If, on the other hand, a number of sets of concordant twins were found that were unmistakably dizygous, that is, if they were of unlike sex, such a finding would point very strongly toward one of the environmental theories. Of considerable importance, too, would be the finding of one or more sets of monozygous twins of which one was Mongoloid and the other was normal. A finding of this nature would be irrefutable evidence for the presence of an environmental factor in the genesis of Mongolism, since only environment can be responsible for intrapair variations in monozygotic twins. It would thus speak very strongly against an exclusively germ-cell theory, although, at the same time, it would constitute no evidence at all for an exclusively environmental theory.

An examination of the Table shows, however, that from the material at hand no definite conclusions can as yet be drawn regarding the etiology of Mongolism on the basis of twin studies. On the one hand, the number of cases recorded is inadequate and the zygosity diagnosis too uncertain. On the other hand, the main key cases are still missing in the literature, namely, either one or more sets of discordant monozygotic twins, or one or more sets of concordant twins of unlike sex.

It is true that three cases of concordant dizygous twins have been reported in the literature,* and possibly a fourth.[28] With the knowledge, however, of the many pitfalls inherent in the determination of zygosity, these cases can be regarded only as probably dizygous and not certainly dizygous. Yet these three or four cases are of the utmost importance, since it is upon these that all the arguments against the germ-cell theories are based as being inconsistent with such a finding.

Thus, the hereditary theory is considered as inconsistent with this finding because of the relative proportion in the literature of concordant dizygotic twins, namely, 3, to discordant dizygous twins, namely, 65, which is about 5%. If this theory were true, this proportion should be much lower, namely, closer to the proportion of sibships with two members affected to the sibships with only one member affected.[27] However, whereas Mongolism is such a frequent condition, familial incidence of Mongolism is very rare, probably less than 1% of affected sibships.[3] Up to 1949 only 49 families had been recorded in the literature in which Mongolism occurred in more than one sibling.[4]

The gametic mutation theory is considered inconsistent with the finding of concordant dizygotic twins because spontaneous gametic mutations are such rare occurrences that they could hardly be expected to occur simultaneously in two different ova of the same person in the three or four recorded instances.[27] This argument is, however, not entirely correct, since mutations occur not only in the oocyte stage but they may and do also occur at earlier points in oogenesis. Mutations occurring at the oogonia stage or earlier could, therefore, result in the same mutation being present in two or more different ova. These might, eventually mature simultaneously and give rise to dizygotic twins that both represent the new mutation.

The defective ova theory is also considered inconsistent with the finding of concordant dizygotic twins, because, according to Jervis,[27] the relative frequency of such cases (3) as compared with the frequency of discordant dizygotic twins (65) is too high. On the basis of statistical probabilities Jervis [27] shows this to be improbable.

From the foregoing it is evident that although, on the basis of the material at hand,

* References 25-27.

no definite conclusions can as yet be drawn regarding the etiology of Mongolism, the possibilities of elucidating this problem on the basis of twin studies are very great indeed. What is required in order to arrive at a solution of the problem is a much larger number of cases of Mongolism in one or both of twins, provided they are adequately studied in respect to their zygosity.

SUMMARY

Three cases of Mongolism in twins are reported. Two were sets of unlike-sex twins of whom the boy in each set was Mongoloid and the girl was normal. The third was a set of probably dizygous, like-sex male twins, of whom one was normal and died at the age of one month, while the Mongoloid survived.

The importance of accurate zygosity diagnosis is stressed, and the methods employed for that purpose as well as their shortcomings are mentioned. The bearing that the study of Mongolism in twins may have upon the elucidation of the problem of the etiology of Mongolism is reviewed.

Dr. Abraham Levinson, Director of The Dr. Julian D. Levinson Research Foundation and Chief-of-Staff of the Children's Division of the Cook County Hospital, gave advice and criticism in the preparation of this paper.

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Bacteriologic Studies of Pulmonary Infections in Patients with Poliomyelitis

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The development of pneumonia is still a common and sometimes fatal complicating illness in debilitated patients. Poliomyelitis, by causing dysphagia and paralysis of the respiratory muscles, frequently predisposes to the development of a secondary bacterial pneumonia. This additional respiratory stress and toxemia often appears to be the cause of death among patients who might otherwise be expected to survive. During the summer and fall of 1952, we had an opportunity to study the pathogenesis and prophylaxis of pneumonia in 72 patients suffering from poliomyelitis with varying degrees of respiratory paralysis. The results of bacteriologic observations of material obtained from the respiratory tracts of these patients are presented here. The effects of various antibiotics in the prevention and treatment of these bacterial infections have been reported,[1] and the correlation of the bacteriologic data and the pathologic findings in fatal cases will be reported in a subsequent paper.[2]

METHODS AND MATERIALS

All the patients observed in this study were hospitalized at the Chicago Municipal Contagious Disease Hospital and had manifestations of paralytic poliomyelitis involving the medullary and spinal segments. The great majority of these patients required a mechanical respirator to compensate for respiratory failure, and each had had a tracheotomy. Secretions for cultures were taken from nose, throat, and trachea at the time of tracheotomy and at intervals during the course of the illness. If the patients died, cultures were obtained at autopsy from the lungs, regional lymph nodes, and spleen. Because of the rapid shifts in the course of the disease, strict bacteriologic control of antibiotic therapy was impossible. Accordingly, many of the patients were given one or more antibiotics empirically at some time during the course of their illness.

At the time tracheotomy was performed, a sterile cotton swab was inserted through the incision into the trachea and coated with secretions for cultures. Immediately, or within a few hours following tracheotomy, cultures were made from the nose and throat. Tracheal secretions were obtained for culture on the day following tracheotomy and once or twice during the subsequent week. Additional cultures were usually taken twice a week during the first two weeks following tracheotomy and once a week thereafter. When death was considered imminent, cultures were made of the trachea within 12 hours prior to death. Material for culture was also obtained, when possible, before antibiotic treatment was changed.

At the time of autopsy, secretions from each lobe of the lung, the regional lymph nodes, and the spleen were sealed in individual glass jars and preserved at —10 to —20 C. Autopsies were usually performed in the evening, and the next morning the specimens were removed from the freezer and thawed at room temperature and the surface was seared with a hot metal spatula. To obtain material for culture a sterile metal loop was inserted to the center of these specimens and rotated.

Bacteriologic procedures were the same for all of the above specimens. Each sample recovered was streaked on agar plates containing 10% human blood, heated blood (chocolate agar), or eosin methylene blue. In addition, a plate of Saboraud's agar and a tube of thioglycolate broth were inocu-

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lated. In some instances, 1 cc. of 95% alcohol was flooded over the surface of a blood agar plate in order to reduce swarming of Proteus vulgaris and to facilitate isolation of other organisms. After the initial cultures from the tissue sections were obtained, they were washed with a few milliliters of ether to suppress the growth of Gram-negative bacilli, and another loopful of material was obtained and recultured on the media specified, except the eosin methylene blue agar. The Sabouraud's agar was incubated at room temperature for 14 days. All other cultures were incubated at 37 C for at least 48 hours.

A Gram stain was made from the thioglycolate broth after 48 hours' incubation, and the contents were then preserved at —10 to —20 C. In a number of cultures streptococci and a few Gram-negative rods were found in the thioglycolate broth but not on the aerobic plates. When this occurred, the cultures from the thioglycolate broth were transferred to an aerobic 10% human blood agar plate. In all instances these organisms grew out on the blood agar plate.

Pure cultures were obtained by transferring organisms from individual colonies on the plates to tryptose phosphate broth, or in the case of the staphylococci and streptococci, to blood broth. The isolated cultures were identified by colony and cell morphology, staining characteristics, and biochemical reactions. In addition, staphylococci were characterized according to hemolysis of human red blood cells, pigmented production, coagulase, and the presence of an alpha hemolysin in the culture supernatant. The minimal inhibitory concentrations of penicillin, chlortetracycline, erythromycin, and carbomycin were determined by the tube-dilution method for all staphylococci. Phage lysis, which was attempted on these organisms several months after isolation, was unsuccessful. Staphylococci were considered to have originated from the same strain if they were similar in coagulase production, if the minimal inhibitory concentration of penicillin was the same within a fourfold dilution range, and if the sensitivities to the other antibiotics were the same within a twofold dilution. These criteria have been shown to be about 80% accurate when organisms are classified as the same and 75% acurate in determining strains which are different.[3]

OBSERVATIONS

Tracheal cultures were obtained at the time tracheotomy was performed on all except 3 of the 72 patients studied. Among the 69 from whom cultures were made, 46 patients (66%) showed bacterial growth, but cultures from 8 of these were sterile on the second attempt, and cultures from 2 additional patients were sterile on both the second and third attempts. Among 23 patients whose initial tracheal secretions showed no growth, 13 had negative cultures on the second examination, and 8 of these patients had negative cultures on both the second and the third examinations.

Table 1 shows the frequency of infection of the lungs at autopsy. Among 19 patients whose initial tracheal secretions yielded bacteria on culture, the postmortem cultures of the lungs at autopsy were positive in 16 (82%). Among six patients whose initial tracheal cultures were negative, the cultures from the lung at autopsy yielded bacteria in three. This difference between rates is not statistically significant. In two of the patients in the latter group, however, bacteria were recovered from only one lobe of the lung. In contrast, among the 16 patients with positive initial tracheal cultures and positive lung cultures at autopsy, bacteria were cultured from more than one lobe of the lung in 15. This difference in incidence of involvement of several lobes is statistically significant. (χ-square = 5.2). Furthermore, the one patient whose tracheal culture was initially negative and who had multilobar infection at autopsy was observed for 10 days before death, and all of the tracheal secretions obtained after the initial one were infected.

Of the three patients who had positive initial tracheal cultures and negative lung cultures at autopsy, one had a negative tracheal culture on the second culture and

TABLE 1.—*Correlation of Incidence of Infection in First Tracheal Culture with Incidence of Infection in Lungs at Autopsy*

		Cultures of Lung at Autopsy	
1st Tracheal Culture	Total No. Cultured	No. with Bacteria in Lung	No. with Bacteria in More Than 1 Lobe of Lung
Infected	19	16	15 *
Sterile	6	3	1 *

* The difference between the incidences of multiple-lobe involvement was statistically significant. χ-square (Yates modification) = 5.2.

TABLE 2.—*Incidence of Genera of Various Micro-Organisms Found in the Respiratory Tract of Tracheotomized Patients with Poliomyelitis*

Organism	Nose	Throat	First Tracheal Cultures	All Tracheal Cultures	Lungs at Necropsy
No. of cultures performed	61	61	69	250	27
	Per Cent of Cultures Performed from Which the Organism Was Isolated				
Micrococcus pyogenes var. aureus	73	45	36	48	48
Streptococcus Viridans	16	67	17	9	11
Enterococci	9	10	10	20	15
Diphtheroids	5	10	10	9	8
Escherichia coli	0	2	1	3	15
Pseudomonas	0	10	1	18	11
Aerobacter aerogenes	17	18	10	25	22
Proteus	2	2	3	15	22
Neisseria	10	43	9	5	7
Yeasts	3	5	6	7	7
None	..	..	34	23	26

another had negative tracheal cultures on the second and third cultures. In neither patient did the tracheal cultures again become positive before death. The third in this group had only a few unidentified Neisseria in the initial tracheal culture and died shortly afterwards.

Table 2 indicates the organisms that were cultured from the nose, throat, trachea, and lungs. A Staphylococcus was present in 73% of the nasal cultures, whereas Aerobacter aerogenes, the second commonest micro-organism, was found in only 17%. A viridans Streptococcus was the commonest organism found in the throat (67%), although Staphylococcus (45%) and Neisseria species (43%) were frequently present. In the trachea, Staphylococcus (48%) and A. aerogenes (25%) were the commonest bacteria. That the flora changes qualitatively following tracheotomy was clear from comparison of the distribution of organisms obtained from the trachea on initial culture as compared with subsequent cultures. Thus there was a significant decrease in the incidence of sterile tracheal cultures from that in the initial culture to that in subsequent cultures (χ-square = 3.9). The incidence of viridans Streptococcus also decreased (χ-square = 7.44). On the other hand, each of the following genera showed a significantly increased incidence: Staphylococcus (χ-square = 4.62), enterococcus (χ-square = 5.19), Pseudomonas (χ-square = 15.1), A. aerogenes (χ-square = 9.7), and Proteus (χ-square = 9.1). The percentage distribution of organisms in the lungs reflected these changes; thus, a Staphylococcus was present in 48%, A. aerogenes in 22%, and Proteus species and enterococcus in 20%, and a Pseudomonas in 11% of the autopsies. Escherichia coli was found in the lungs in 15% of the autopsied patients but in the trachea in only 3% of the cases and may have been a very late invader.

In all, 85% of tracheal cultures showed some change when follow-up cultures were taken. During the course of the study it became evident that while in some cases the flora changed within a few hours, in a number of instances an organism persisted for weeks in a patient's trachea. This was particularly true during the chronic phase of the illness.

An attempt was made to determine the source of the bacteria found on the first tracheal culture and in the lungs at autopsy.

TABLE 3.—*Bacteria Cultured from Lower Respiratory Tract for Which a Likely Source was Found*

Organism	1st Tracheal Culture: No. of Strains Studied	1st Tracheal Culture: No. in Which Similar Organisms Were Found Simultaneously in Upper Respiratory Tract	Lungs: No. of Strains Studied	Lungs: No. in Which Organisms Found in Antemortem Cultures
Micrococcus pyogenes	15	6	7	6
Streptococcus Viridans	10	9	2	2
Enterococci	4	4	3	3
Diphtheroids	5	4	2	2
Escherichia coli	1	1	2	0
Pseudomonas	1	1	..	..
Aerobacter aerogenes	5	5	3	3
Proteus	2	2	4	3
Neisseria	2	2	..	..
Yeasts	2	1	2	2*
Total	47	35	25	21

* One of the organisms was found in an antemortem blood culture.

TABLE 4.—*Bacteria Found in the Lungs and the Incidence in Which They Were Found in Previous Cultures of the Trachea and/or the Upper Respiratory Tract*

Organism	No. in Lung	No. in Last Tracheal Culture	No. in Other Tracheal Cultures But Not in Last Tracheal Culture	No. in Nose and/or Throat But Not in Trachea
Micrococcus pyogenes	6	3	1	1
Alpha Streptococcus	2	0	0	2
Enterococci	3	3	0	0
Diphtheroids	2	2	0	0
Escherichia coli	2	0	0	0
Pseudomonas	0	0	0	0
Aerobacter aerogenes	3	1	1	1
Proteus	3	1	2	0
Neisseria	1	0	0	0
Yeasts	0	0	0	0
Total	22	10	4	4

The data in Table 3 are derived from a detailed study of 67% of the organisms, since a few were incompletely studied and a large number were lost in a laboratory accident involving the stored cultures before more than a species classification had been completed. However, as is indicated, of the strains which were obtained from the initial tracheal culture and concerning which sufficient data were available to enable the source to be identified, 76% were present in a nose and/or a throat culture which were taken at the same time as the tracheal culture. Also, 84% of the 25 strains which were cultured from the lungs at necropsy and for which adequate data were available had been obtained previously from the trachea, throat, and/or nose during life. The four bacterial strains recovered from the lungs which were not isolated from the antemortem cultures were E. coli in two cases and Staphylococcus and Proteus in one each.

Table 4 lists the numbers and types of bacteria found in the lungs of patients who had tracheal cultures taken within 12 hours of death. Of 22 organisms cultured from the lungs, 10 were obtained in the last tracheal culture taken a few hours before death. Four additional strains were found in other tracheal cultures, but not in the last culture. Another four organisms were found in the lung which were not found in the tracheal cultures taken but were obtained from the nose and/or throat. Therefore, 18 of 22 organisms found in the lung (80%) were also present in the trachea, nose, or throat at some time prior to death. Sixty-seven per cent of the infections in the lungs were mixed infections.

Table 5 compares the organisms found in the regional lymph nodes and spleen with those found in the lungs. All but one strain of the organisms (18 among 19) found in the regional lymph nodes were also cultured from the lung. Of 12 strains found in the spleen, 9 were also present in the regional lymph nodes and lungs. Although Micrococcus pyogenes var. aureus was found in the regional lymph nodes of six autopsied patients, none of these strains were present simultaneously in the spleen. Gram-negative rods and enterococci cultured from the regional lymph nodes were frequently present in the spleen.

TABLE 5.—*Correlation of Bacteria Present in Regional Lymph Node and Spleen with Those Present in Lung*

	Organism Cultured from			
	Lymph Node		Spleen	
Organism	No. Cultured	No. in Which Same Organism Was Found in Lung	No. Cultured	No. in Which Same Organism Was Found in Lung and/or Regional Lymph Node
Micrococcus pyogenes	6	5	1	0
Alpha Streptococcus	0	0	0	0
Enterococci	4	4	2	2
Diphtheroids	0	0	1	0
Escherichia coli	2	2	1	1
Pseudomonas	3	3	1	1
Aerobacter aerogenes	1	1	0	0
Proteus	2	2	2	2
Neisseria	0	0	2	1
Yeasts	1	1	1	1
Total	19	18	12	9

One patient had Candida stellatoidea in her lungs, regional lymph nodes, and spleen.* This yeast was present in an antemortem blood culture but not in cultures from the nose, throat, or trachea. In three other patients, an organism was cultured from the blood and trachea simultaneously. These were a Pseudomonas species once and a Staphylococcus twice

The great majority of staphylococci isolated from the upper and lower respiratory tract produced beta hemolysis on human blood and produced a yellow pigment. Sixty-three strains of staphylococci isolated from the upper respiratory tract (nose and throat) were tested for coagulase and alpha-hemolysin production. From Table 6 it is seen that 44% of these organisms were coagulase-positive and 25% were alpha-hemolysin producers. Forty-three per cent of the organisms which were coagulase-positive did not produce alpha hemolysin. None of the organisms from the upper respiratory tract which were coagulase-negative produced alpha hemolysin. One hundred sixty-one strains of staphylococci were isolated from the lower respiratory tract (trachea and lungs). Sixty-one per cent were coagulase-positive, and 58% of them produced alpha hemolysin. Both of these figures are significantly higher statistically than the corresponding rates for the organisms from the upper respiratory tract. Only 3% of the organisms which were coagulase-positive did not produce alpha hemolysin, a significantly lower incidence than that for isolates from the upper respiratory tree. None of the organisms which were coagulase-negative produced alpha hemolysin.

TABLE 6.—*Alpha Hemolysin and Coagulase Tests on Micrococci Obtained from Poliomyelitis Patients*

	Upper Respiratory Tract	Lower Respiratory Tract
Total number of organisms.....	63	161
Per cent coagulase-positive.....	44	61
Per cent alpha-hemolysin-positive	25	58
Per cent coagulase-positive and alpha-hemolysin-negative	43	3
Per cent alpha-hemolysin-positive and coagulase-negative.....	0	0

Of 25 patients with negative initial tracheal cultures, 12, or 48%, had multiple episodes of vomiting associated with dysphagia during the course of illness prior to tracheotomy, whereas 33 of 44 patients (75%) who had positive initial tracheal cultures had multiple episodes of vomiting in association with dysphagia during the course of illness prior to tracheotomy. This difference is statistically significant (χ-square = 5.5).

Of 44 patients who had positive initial tracheal cultures, 14 had rhonchi, rales, or a history of aspiration of mucus. Only 1 of the 25 patients with initial negative tracheal cultures had rhonchi in the chest prior to tracheotomy, and none of these had rales or a history of aspiration. Eighty-five per cent of the patients who had rhonchi or rales had vomiting associated with dysphagia.

COMMENT

Pulmonary infections in the form of pneumonia or atelectasis associated with infection are common in patients with poliomyelitis who have difficulty in breathing, coughing, and swallowing because of muscular weakness. In the present study we have attempted to determine the route by which the bacteria enter the lower respiratory tract. In other studies we will report on the etiologic significance of these organisms in the pulmonary infections observed at postmortem examination,[2] the role of antibiotics in the control of these infections,[1] and the spread of the bacteria on the hospital ward.[4]

Since the available evidence indicates that the trachea is normally sterile,[5] it is significant that two-thirds of our patients had infected lower respiratory passages by the time tracheotomy was performed and that such infections were correlated with extensive pul-

* Dr. Esther Meyer, of the Department of Bacteriology, University of Illinois, cooperated in identifying this organism.

monary involvement among the patients who were autopsied.

Because the strains found at the time of tracheotomy were identical with those in the nose and throat in 76% of the patients tested, it seems certain that most of the original tracheal infection was endogenous. The higher incidence of vomiting prior to tracheotomy among the infected patients, particularly in those from whom enterococci and the Gram-negative rods were isolated, indicates that aspiration of vomitus was an important factor in the original tracheal infection. Once the tracheotomy was established, it was the rule for further infection to occur, as shown by the fact that 85% of the subsequent cultures showed some change in flora. There was a tendency for more varied infections to occur among those patients who died and for mixed infections to be predominant in the autopsied patients. From a comparison of the distribution of strains on the initial tracheal culture with those found in the subsequent cultures, it is clear that strains of Pseudomonas, Proteus, enterococcus, and the more pathogenic staphylococci increased in frequency. It is likely that, in some cases at least, they entered through the open tracheotomy wound. On the other hand, the less pathogenic viridans Streptococcus decreased markedly.

The distribution of organisms from the infected lungs at autopsy reflected rather accurately this increase in the more virulent organisms with the passage of time. It was clearly shown that most strains in the lungs at autopsy had been previously found in the respiratory tract, and a large number were in the trachea shortly before death in spite of antibiotic treatment.

The extent of the infections which occurred in these patients was reflected by the demonstration of positive blood cultures in several and the isolation of the pulmonary strain from the regional lymph node in 18. Pathologic studies have indicated the importance of the organisms isolated in the causation of pulmonary infections.[2]

From the above evidence of the constant increase of tracheal infections with the more pathogenic strains, even though many infections are endogenous, it is apparent that asepsis at the time of surgery and in the care of patients with tracheotomy openings is a very important prophylactic measure against respiratory infections in these patients. Moreover, since the upper-respiratory-tract flora is important in the endogenous infections, bulbar poliomyelitis patients, from the time of their admission to the hospital, should be protected from personnel carrying antibiotic-resistant pathogens. The early use of Levin tubes in all patients who have dysphagia associated with vomiting would probably reduce the number of enterococci and Gram-negative rods in the respiratory tract.

SUMMARY

The pathogenesis of bacterial pulmonary infections was studied in 72 patients with poliomyelitis who had been tracheotomized because of the spinal cord and brain stem lesions.

Pathogenic micro-organisms appeared to enter the lower respiratory tract of these patients directly from (1) the nose and throat, (2) the gastrointestinal tract, by vomitus, and (3) the external environment, through the tracheotomy opening.

A staphylococcus was present in 73% of the nasal cultures, whereas viridans Streptococcus (67%), staphylococci (45%), and Neisseria (43%) were predominant in the throat and staphylococci (48%) and Aerobacter aerogenes (25%) were the commonest bacteria in the lower respiratory tract.

The infections which occurred in the lower respiratory tract were usually of mixed etiology.

Bacteremias occurred in three of these patients. It is possible that in many patients the descending infection from the upper respiratory tract invaded the lungs and then entered the blood stream via the pulmonary vessels or lymphatic system. In some patients it is possible that bacteria from other foci than the

respiratory tract entered the blood and infected the lungs by this route.

In a number of these patients the additional stress imposed by the infection of the lower respiratory tract was sufficient to precipitate death.

Prophylactic measures are discussed.

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CORRECTION

In the review of "Die Pathogenese des Icterus gravis," by Helmut Patzer, in the April, 1955, issue of the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN (p. 509) the name of the publisher was incorrectly given. This book is published by VEB Georg Thieme, Hainstrasse 17-19, Leipzig C 1, Germany.

According to information received too late for inclusion in the news item "Survey of Pediatric Education in Latin America" (May issue, p. 605), the survey will be begun in July, 1955. Hence the statement "will take place in the fall of 1955" (line 6) should be changed to read "will take place in the summer and fall of 1955."

Oxalosis

Report of a Case with Review of the Literature

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Over 100 years ago the medical profession in Europe and America became interested in the presence of calcium oxalate crystals in human urine. It was known that this substance was liable to form urinary calculi, and it was suspected that its excretion in the urine might indicate a metabolic disorder. Largely under the influence of Prout * and Golding Bird [3] the concept of an "oxalic acid diathesis" was established, and a variety of neurasthenic, dyspeptic, and rheumatic symptoms was attributed to this.† Later, attempts were made to support the diagnosis of the condition by demonstrating abnormally high levels of oxalate in the blood and urine of the patients; the terms "oxalemia" and "oxaluria" were coined. In the present century, Loeper ‡ and his associates in France have been particularly active in the investigation of the suspected metabolic disorder and in attempts to maintain "oxalemia" as a clinical entity. There is a considerable literature on the subject, particularly in France and Italy, and recent reviews are available.§

In the English-speaking countries and in Germany the syndrome of the oxalic diathesis with its varied symptomatology appears to have fallen into disrepute and has gradually disappeared from medical textbooks. It is accepted that normally 10 to 30 mg. of oxalic acid is excreted daily in the urine in the form of oxalates and that most of this is derived from oxalate-containing foods, such as spinach, rhubarb, and coffee, while a small proportion is probably endogenous.‖ The finding of calcium oxalate crystals in the urine is also considered a normal phenomenon. Abnormally, in some persons, such urinary oxalates may precipitate extensively and form gravel and calculi. The reason for this precipitation is obscure. Most investigators consider that in general the process is not closely related to the concentration of oxalates in the urine but may rather be dependent on other factors, such as the lack of protective colloids or electrolytes.¶ It is usually held that there is insufficient evidence for the occurrence of a primary metabolic error associated with a persistently increased output of endogenous oxalate,[18] and the concept of any special set of systemic symptoms associated with such a disorder is no longer maintained.[19]

Evidence for the existence of "oxalemia" as a metabolic disorder could be based on biochemical or pathological findings. The data concerning biochemical changes consist largely of estimations of oxalate concentration in the body fluids of patients alleged to suffer from the disease. Unfortunately, the accurate determination of oxalate levels in urine and, particularly, in blood is difficult, and much of the biochemical work has been criticized on technical grounds.# Regarding pathology, French workers claim to have found calcium oxalate crystals very occasionally in patients with "oxalemia," for instance, in tophi [10] and in the cerebrospinal

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* References 1 and 2.

† References 4-7.

‡ References 8-10.

§ References 11-13.

‖ References 14 and 15.

¶ References 12, 16, and 17.

References 14, and 20-22.

fluid [23] but the evidence is rather unconvincing. On the other hand, it may be noted that such crystals have at times been encountered in the body as a surprise finding; for example, in one instance their presence was demonstrated in the tunica media of a middle cerebral artery,[24] and they are reported to be of frequent occurrence in sections of the thyroid gland.[25]

The pathology of "oxalemia" could reasonably be expected to be similar to the effects of chronic oxalate poisoning. Animal experiments demonstrating such effects have been performed by a number of investigators, particularly in Germany. Kobert and Küssner [26] were among the first to point out that the most characteristic morbid anatomical changes in both acute and chronic oxalate poisoning occur in the kidneys; they showed that the renal tubules tended to be filled with oxalate crystals. These findings were confirmed by several other workers. Ebstein and Nicolaier [27] produced chronic oxalic acid poisoning in rabbits and dogs and gave a careful description of the renal changes produced. Doubly refractile crystals, soluble in hydrochloric but not in acetic acid, tended to fill the lumen of the renal tubules, particularly in the cortex, and were considered to consist of calcium oxalate. The epithelium of the tubules in which the crystals were situated was often compressed and sometimes even necrotic. The glomeruli were generally unaffected. Using oxamide instead of oxalic acid, the authors also produced urinary calculi in animals. In the present century it has been emphasized that the kidney changes in chronic oxalate poisoning consist not only of crystal deposition but also of a degree of nephritis,[28] which causes functional impairment of the kidneys. The effects of oxalic acid can be duplicated with ethylene glycol, as this is oxidized to oxalic acid in the body.[29]

It appears that these characteristic renal changes have never been demonstrated in the patients alleged to suffer from "oxalemia." On the other hand, they form the main finding in a condition which is gradually emerging as a rare cause of progressive renal failure, particularly in children, and which may more truly represent a defect of oxalate metabolism. The term "oxalosis" has been suggested for this condition.[30]

REVIEW OF REPORTED CASES OF IDIOPATHIC RENAL PARENCHYMATOUS OXALATE DEPOSITS

At the annual meeting of the French Association of Urology, in Paris, October, 1925, Dr. Lepoutre,[31] of Lille, discussed the case of a child who suffered from multiple urinary calculi with infiltration of the renal parenchyma by crystalline deposits. Unfortunately, only a brief abstract of this report is available. It states that in a child of 4½ years who had multiple urethral, ureteric, and bilateral renal calculi, a biopsy showed a renal parenchyma stuffed with crystalline concretions of calcium oxalate. This was considered to be the clinical equivalent of the animal experiments of Ebstein and Nicolaier; yet no abnormal intake of oxalate was recorded.

In 1941, Laas [32] reported the presence of calcium oxalate crystals in the renal tubules of a man of 25 years who had died from peritonitis after an abdominal gunshot wound. This was an incidental autopy finding, and the case differs from the others in this group in respect of the absence of known renal symptoms and the presence of necroses of collecting tubules at the apices of the papillae, where few or no crystals were seen.

In 1947, Vischer [33] published the case of a boy who was admitted to hospital at the age of 10½ years suffering from diphtheria of 16 days' duration complicated by palatal paresis. Chvostek's sign was found to be positive. The urine contained albumin and a deposit of leucocytes, variable amounts of epithelial cells, and scanty red cells. The red cells were seen only during the first 10 days of observation, and the albuminuria was thought to be diminishing during the 8 weeks in hospital. However, 2½ months later the boy was readmitted in advanced renal failure. He died after 10 days, aged nearly 11 years. Autopsy showed the kidneys to be small, firm, and of half the normal weight, with a pale and granular surface. On section they

were gritty, and numerous crystalline foci, up to 3 mm. in diameter, were visible, while the cortex was thinned. Pelvis and ureter appeared normal. Microscopic examination revealed massive deposition of calcium oxalate crystals in the renal parenchyma, associated with chronic nephritis. Some of the crystals were clearly situated in dilated tubules, and the deposits were somewhat more marked in the cortex than in the medulla. The author considered that the renal changes could best be explained as due to the diphtheria, but it is evidently possible that their onset preceded that disease.

In 1950, Davis, Klingberg, and Stowell [34] reported an even more remarkable case. This was a boy who was first admitted to hospital at the age of 3 years, having had polydipsia and polyuria for three to four months, slight dysuria for about one month, and milky urine for two to three weeks. He was found to pass a sterile urine containing 1+ albumin and many white cells. Blood tests revealed normal nonprotein nitrogen, serum protein, chloride, and bicarbonate concentration, and the urea-clearance test was normal. X-ray examination showed calcification and calculi in both kidneys. Three months later, the child began to pass gravel and stones, and the latter were found to consist of 78% calcium oxalate. Oxalate-containing foods were prohibited, and various acidifying agents and large amounts of vitamin A were administered. However, the condition was slowly progressive. The nonprotein nitrogen level first became elevated at the age of 6½, and rapid deterioration occurred at 12 years. He finally died in uremia.

At autopsy the kidneys resembled those described in Vischer's patient, but they also contained many small hard irregularly-shaped calculi in the pelves and calyces, all light brown on the outer surface and white inside. Microscopy revealed advanced chronic nephritis with many focal areas containing crystalline deposits and also a few bluish-staining foci resembling calcium deposits. Chemical studies showed the stones to be 71% or 83% calcium oxalate, while the crystals also had the properties of that substance. A further finding in this case was the presence of foci of similar crystalline material in sections of rib, femur, and vertebrae. The four parathyroids were somewhat enlarged.

In 1951, Mulloy and Knutti [35] presented the case of a male infant in whom the condition rapidly led to a fatal termination. He was admitted at the age of 4½ months, having had vomiting for 10 days and convulsions for 1 day. On physical examination he was underweight, though well developed, and had a positive Chvostek sign. The urine was sterile but contained 3+ albumin and white and red cells in the deposit. Blood tests indicated the presence of renal failure with anemia and uremia. X-ray examination showed a diffuse distribution of radiopaque material throughout both kidneys. The child developed progressive acidosis, had further convulsions, and died after two and one-half weeks. Postmortem examination showed kidneys containing oxalate deposits. Aggregates of crystalline material were noted within the collecting tubules and distributed about the proximal convoluted tubules. In some areas tubule structure seemed to have disapeared, and an increase of fibrous interstitial tissue was noted about the crystalline material. However, the glomeruli were normal. X-ray diffraction examination of dried kidney tissue identified the crystals as calcium oxalate monohydrate. The one parathyroid which was found showed simple hyperplasia. Bone sections are not mentioned.

In 1952, Ying Chou and Donohue [30] recorded a further case, which resembled that of Davis and her colleagues. This was a boy who had recurrent hematuria from the age of 23 months and started passing calculi two months later. After another two months he was admitted to hospital, where his urine was found to contain a faint trace of albumin, as well as many red cells, a moderate number of pus cells, and calcium oxalate crystals. X-ray examination revealed moderate bilateral hydronephrosis, a small calculus in the right renal pelvis, and larger stones in both ureters. The calculi were removed surgically and found to consist chiefly of calcium oxalate. However, further stones formed

and the urinary infection persisted. The child was treated with an alkali-producing diet low in oxalates. At the age of 6½ years he had three episodes of ureteral colic within a week, and three months later he was taken into hospital after a transient left hemiparesis. Laboratory tests now showed severe renal insufficiency with acidosis. Left hemiparesis recurred, and his general condition deteriorated rapidly. Another calculus was removed from the left ureter and was found to contain 60% of calcium oxalate. The child died in uremia at 6 years and 11 months. At autopsy the kidneys resembled those of the previously cited patients. The renal parenchyma was reduced and showed extensive crystal deposits. Moderate bilateral hydronephrosis was noted, but there was only one brown ovoid calculus in a lower right major calyx, accompanied by pus, while the left pelvis was free of pus and calculi. Microscopically, there was diffuse intratubular deposition of calcium oxalate crystals, with extensive tubular atrophy, affecting particularly the proximal convoluted tubules. Slight interstitial fibrosis and lymphocytic infiltration were present. The glomeruli were relatively normal. Two parathyroids were identified and appeared slightly enlarged, but they were histologically normal. Oxalate crystals were also found extensively in bones, and occasional rosette-like deposits were encountered in the heart, lungs, spleen, thymus, and pituitary.

Finally, in 1953, Newns and Black [26] published details of a case diagnosed during life. The patient was a girl who had been in normal health until the age of 2 years, when she passed several small urinary calculi and was found to have albuminuria. It was of particular interest that this child's older brother had died of renal failure with multiple calcium oxalate stones at the age of 8 years; further, a maternal greatuncle was said to have passed five renal calculi. The girl was examined in the hospital at the age of 2 years and 4 months, when she was somewhat pale and of only moderate nutritional state but otherwise presented no abnormal signs. Her blood pressure was 130/85. The urine was acid, free of protein, and sterile; the deposit contained 40 to 50 WBC per high-power field; occasional specimens contained calcium oxalate crystals; there was only a very faint precipitate with Sulkowitch reagent; cystine was absent, and urine chromatography showed a normal amino acid pattern. The urine clearance was 55.8% and 65% of average normal. Gravel passed in the urine consisted entirely of calcium oxalate. The urinary excretion of oxalic acid was measured on four days and was found to range from 65 to 122 mg. of free oxalic acid and from 95 to 182 mg. of free and combined oxalic acid per 24 hours, while one adult control subject excreted only 22 mg. of free and combined acid. An x-ray film of the abdomen showed dense calcification in the medullary regions of both kidneys and also some small separate calculi. An intravenous pyelogram and skeletal survey revealed no abnormality. No crystals were found on examination of bone marrow. Two calcium balance tests showed a normal retention of calcium, with rather low figures for urinary calcium excretion. The patient's progress was followed. At the age of 5 years she was still in good health and presented no evidence of renal failure.

It is now intended to report a further case, which presents several interesting features.

REPORT OF A CASE

Lorraine C., a white girl, was the eldest of three children. Her parents were not consanguineous. Her father had passed a renal calculus at the age of 33 years but had been well in the ensuing nine years. Her younger sister had albuminuria during an illness of three weeks' duration at the age of 5 years, but x-ray films at the time showed no calculi and later urine tests revealed no abnormality. No other members of the family were known to have had any relevant disease.

The patient's birth weight was 8 lb. 4 oz. Her initial development was normal, and the weight had risen to 25 lb. at one year. Her diet was normal and rarely contained foods rich in oxalates, except for a moderate amount of chocolate which she took during her school period. During that time, however, she also generally consumed about 3 pt. (1½ qt.) of milk daily and thus had a fairly large intake of calcium, which is likely to reduce the absorption of oxalic acid by combining with it to form insoluble calcium oxalate in the alimentary tract.

At the age of 2 years, her appetite appeared to decrease and she became somewhat irritable. At 4 years, she had an attack of gross hematuria with a cold. At 5 years, she had nausea, vomiting, headache, and nocturia and developed a bout of fever with abdominal pain. X-ray examination revealed that both kidneys were loaded with stones; there were also calculi in the ureters. After a month she was admitted to her local hospital, where she was found to be somewhat underdeveloped but to present no other abnormal physical signs. Her blood pressure was normal. The urine was acid; its specific gravity varied from 1.007 to 1.024, and it always contained a trace of albumin. Its deposit showed many pus cells, but no casts, crystals, or red cells were noted. Cultures repeatedly yielded Escherichia coli. An intravenous pyelogram demonstrated fair dye concentration but multiple calyceal hydronephrosis. Roentgenograms of the long bones were reported to demonstrate arrested rickets, while bone density and epiphyseal development were normal. Her blood nonprotein nitrogen (NPN) at that time was 34 mg. per 100 cc.; the serum calcium varied from 6.9 to 10.5 mg., and the serum phosphorus was 5.7 mg. per 100 cc. The serum alkaline phosphatase was 3.4 to 5.1 Bodansky units. The serum CO_2 content fluctuated between 38 and 42 vol. per 100 cc. (17 to 19 mEq/L.). The uric acid and creatinine concentrations in the blood were normal, and the Wassermann reaction and tuberculin patch test were negative. The phenolsulfonphthalein (PSP) clearance was only 21% in the first 15-minute specimen, but it reached 78% in two hours. She was treated medically with an acid-ash diet, which included cranberry juice, and with ammonium chloride and methenamine mandelate (Mandelamine) to keep the urinary pH at 5.5 or less, and she was also given carotene in oil to ensure a good supply of vitamin A. In addition, she received sulfonamides. However, the urine remained infected, and during the following year she passed more than 100 small stones, usually accompanied by flank pain.

At the age of 6 years, she was twice readmitted to hospital and had a right and then a left nephrostomy performed. Marked perirenal fibrosis was found at operation, and the ureters appeared dilated. About 20 stones were removed from the right and 30 from the left renal pelvis. She had now developed an anemia with a hemoglobin (Hgb.) concentration of 57%-64% and a red cell count (RBC) of 3,400,000 to 4,100,000/cu. mm., while her blood NPN was 41 mg. per 100 cc. Her PSP clearance had fallen to 12.5% in the first 15 minutes and 67% in two hours.

Direct and retrograde pyelography showed mild bilateral dilatation of the renal pelvis and considerable dilatation of the ureters. The urine from both ureters was infected. She received blood transfusions, and the acid diet was discontinued. Four months later, dilatation of both ureterovesical junctions was performed, and on retrograde pyelography the previous findings were confirmed. Renal calculi were found to be forming afresh.

At 7 years, she had an acute febrile renal infection due to E. coli. Her blood NPN rose to 83.5 mg/100 cc., and her PSP clearance had fallen to 12% in the first specimen and to 41% in two hours. She was vomiting and received infusions and sulfadiazine. A month later she had four stones removed from the left ureter. After this she had several hospital admissions for blood transfusions, and her urinary infection was treated energetically with chemotherapy. This caused some improvement in her general health, but the urine continued to show many pus cells in the deposit and now contained more albumin (1+ to 3+).

At 13 years, she broke her right forearm after slight trauma while skating. Four months later, a bone in her left forearm was cracked when kicked by another child. X-ray examination revealed decalcification of all bones, with formation of some cyst-like areas, and also extensive calcification in both kidneys with formation of "staghorn" and rounded stones and of amorphous calcareous deposit in the parenchyma. After an intravenous pyelogram there was no visible dye output from either kidney during 30 minutes. Her blood NPN at this time was determined as 82.5 and 86 mg., the serum protein as 5.2 gm. (albumin, 3.6; globulin, 1.59) and the serum cholesterol as 260 mg. per 100 cc. She was transferred to the Babies Hospital for further investigation and treatment.

Physical examination showed an underdeveloped but fairly healthy-looking girl. Her height was 145 cm. (about 2½ S. D. below normal) and her weight 35.2 kg. (about —2 S. D.). Slight acne vulgaris was present on the face, and several pale pigmented nevi were seen on the trunk. Scanty fine axillary hairs and a few pubic hairs were noted. Breast development was considered normal. There was some residual deformity of the right forearm. The blood pressure was 120/70. The liver was palpable for 1 cm. below the right costal margin, and slight tenderness in the costovertebral angle was found on both sides. Otherwise, no abnormal signs were detected.

The laboratory investigations may be briefly listed as follows: Blood Studies: Hgb., 10 gm.; RBC, 4,700,000/cu. mm.; WBC, 15,500, with 78% polymorphonuclear cells. Urine: Specific gravity, 1.010; pH, 6.0; albumin, 2+; 20 WBC per high-power field, and occasional clumps of red cells in the deposit; Sulkowitch test for calcium normal (negative or 1+). Urinary calcium excretion on ordinary ward diet 135 to 208 mg. in 24 hours. Serum sodium, 142 mEq/L.; potassium, 5.3 mEq/L.; calcium, 9.5 mg. and 9.6 mg.; phosphorus, 5.7 to

Fig. 1.—A plain x-ray film of the abdomen at 15 years 2 months shows bilateral fine focal calcification in the kidneys and calculi in the renal pelves and calyces.

7.0 mg/100 cc.; alkaline phosphatase, 9.6 to 11.2 Bodansky units. Blood NPN, 66 mg.; serum protein, 5.6 gm.; cholesterol, 228 mg/100 cc. Serum CO_2 content, 22.4 mEq/L.; plasma chlorides, 111 mEq/L. PSP clearance less than 10% in two hours.

X-ray examination of the skull showed moderate granular osteoporosis of the calvarium and mandible; the lamina dura of the teeth was invisible, and the mandible exhibited cystic changes. The chest film showed areas of rarefaction in the right clavicle and in both scapulae. In the spine there was soft woolly and granular osteoporosis of all vertebrae without evidence of compression. A roentgenogram of the abdomen (Fig. 1) demonstrated extensive bilateral fine renal calcification and also large renal stones which filled the calyces and the major part of the renal pelves. A staghorn stone was present in each pelvis and showed the radiating spicules which Albright * considers characteristic of calcium oxalate (Fig. 2). The long bones exhibited severe osteoporosis, more marked in the terminal than in the central segments of the shafts; the provisional zones of calcification were sharply defined and showed no evidence of rickets; there were deep metaphyseal zones of severe rarefaction affecting the spongiosa as well as the cortex, and these were limited shaftward by wide transverse bands of dimished density suggestive of *Umbauzonen*. Subperiosteal resorption was well seen in the femora and tibiae near the knees (Fig. 3). Clear-cut areas of cystic rarefaction were present in the small tubular bones of the hands (Fig. 4), where they occupied the entire width of the metaphyses, with dilatation of the medullary cavity and corresponding local atrophy of the cortex. Similar changes were present in the feet. There were no signs of fracture except in the left radius. Maturation was slightly delayed. The bony changes appeared characteristic of osteitis fibrosa cystica, and the presence of radiolucent bands in the shafts and of denser insets in the patellae and ilia suggested that the skeletal disease had supervened during the course of bony development.

Cystoscopy and retrograde pyelography confirmed the presence of bilateral hydronephrosis and multiple renal calculi. The bladder appeared grossly normal. Urine from both ureters was infected with organisms of the E. coli group and with Gram-positive cocci.

At that time, the diagnosis appeared to lie between primary kidney disease with renal hyperparathyroidism and primary hyperparathyroidism

Fig. 2.—The staghorn calculus in the left renal pelvis is shown to be composed of radiating spicules characteristic of calcium oxalate.

* References 37 and 38.

Fig. 3.—Film of knees at 13 years 4 months shows osteoporosis with metaphyseal zones of rarefaction, limited shaftward by transverse radiolucent bands (*Umbauzonen*). There is subperiosteal rarefaction. Epiphyseal ossification centers exhibit submarginal zones of diminished density. These marginal changes are also visible in the patella and suggest transitory demineralization during a short period of growth with subsequent recovery.

with secondary renal damage, though the normal serum alkaline phosphatase and urinary calcium were surprising in either case. To rule out the possibility of a primary parathyroid tumor, surgical exploration of the neck was performed. The parathyroids were found to be normal in appearance and position; the left upper one seemed a little larger and darker than the others and was removed but proved normal on section.

After this hospital admission the child's gait became unsteady, and she complained of leg pains, especially at night. She was readmitted for further investigation at the age of 14 years and 4 months. On examination, her blood pressure now was 130/70. The tendon reflexes were hyperactive, with transient patellar and ankle clonus. Chvostek's and Trousseau's signs were negative, and the other findings were unchanged. The hemoglobin concentration had fallen to 7.6 gm/100 cc.; the red cell count, to 2,600,000/cu. mm. The urine pH was 4.5; specific gravity was 1.014; it contained 3+ albumin, and the deposit was packed with white cells. The urinary output of creatinine was 430 mg. (or 12.5 mg. per kg. body weight), of creatine 196 mg. (or 5.7 mg. per kg.), and of phosphorus 406 mg/24 hours. There was no abnormal output of amino acids. Her blood NPN had risen to 115 mg., and the serum phosphorus to 9.7 mg. per 100 cc., while the serum CO_2 content had fallen to 16.5 mEq. and 14.8 mEq/L. The other chemical findings and the roentgenograms showed little change. The patient was given a blood transfusion which caused a febrile reaction. Basic aluminum gel was now given by mouth to reduce intestinal phosphorus absorption.

Subsequently her condition slowly deteriorated. She continued to pass urinary calculi, usually with some pain in the flanks, and she also complained of limb pains. At the age of 14½ years she was again admitted, her hemoglobin concentration having fallen to 6.7 gm/100 cc. She voided an infected acid urine (pH 5 to 5.5), with a specific gravity ranging only from 1.006 to 1.014 and a low ammonia output of 2 to 6 mEq. daily. Her urinary organic acid output varied from 37 to 62 mEq. daily and was thus within normal adult limits. On a low-sodium diet her blood NPN rose from 108 to 162 mg/100 cc. She was given another blood transfusion and was discharged on a normal diet with sodium citrate and aluminum gel.

During her further course she was given occasional transfusions as an outpatient. The urinary calcium amounted to only 33.7 to 60 mg. per day on an ordinary diet, and the Sulkowitch test showed only a trace of calcium in the urine. The urinary phosphorus excretion ranged from 247 to 486 mg.

Fig. 4.—Film of hands at 13 years 4 months shows cyst-like changes in the radii and ulnae and, most conspicuously, in the distal ends of the metacarpals and proximal ends of the phalanges. The carpal bones have submarginal zones of diminished density. There is a fracture in the left radius.

daily. When she was nearly 15 years old she had a further admission because of severe pains in the thighs and inability to walk. Her height was now 141 cm. (3 S. D. below normal), and her weight was 33 kg. (—2.5 S. D.). Her breath was ammoniacal. Both femora and quadriceps groups were tender. Laboratory and x-ray findings were essentially unchanged.

At 15 years and 1 month she began to exhibit hemorrhages in the form of purpura, hematemeses, melena, and hematuria. Her platelets were found to number 130,000/cu. mm. During the following nine months she had 10 further admissions, chiefly for transfusions. At one time she had right chest pains, and these were attributed to osteitis fibrosa cystica, which had now become apparent radiologically in the ribs. The liver gradually became enlarged and tender, and there was persistent tenderness in the costovertebral angles. She complained of nausea, vomiting, headaches, and occasional cramps in her hands in addition to her previous pains. Finally she passed into the terminal stage of renal failure, probably associated with some degree of heart failure. Her blood pressure rose only to about 140/80. In spite of digitalization, blood transfusions, treatment with antibiotics and calcium gluconate, and careful control of her fluid balance, she died at 15 years and 10 months after being in coma for about 2 weeks. Her last blood tests showed the following results: serum calcium, 10.5 mg.; phosphorus, 14.5 mg., and blood NPN, 222 mg/100 cc.; serum sodium, 120 mEq.; potassium. 3.3 mEq.; chlorides, 97 mEq., and CO_2, 7.6 mEq/L.

Postmortem Examination.—Permission for autopsy was restricted to examination of the trunk. External examination showed pallor of skin and mucous membranes, wasting, and some facial edema. The body length was 136 cm., which is normal for a girl of 9 years. Slight brownish pigmentation was noted on the face, arms, shoulders, and lips, and a few pigmented nevi were seen on the trunk. The right nostril and tongue were crusted with blood, and the lips, chest, abdomen, and legs exhibited multiple petechiae. Well-healed scars were present on the neck and in the loins and left iliac fossa. Some fine pubic hair was noted. There was bilateral cubitus valgus with a carrying angle of about 150 degrees.

The serous cavities contained clear straw-colored fluid. About 250 cc. of this was found in the peritoneal cavity; 200 cc., in each pleural space, and 20 cc., in the pericardial sac.

The heart was somewhat enlarged and weighed 285 gm. (normal for patient's body length is about 123 gm.). Hypertrophy of the left and dilatation of the right ventricles were noted. An atheromatous streak was found on the aortic leaflet of the mitral valve. The bases of the aortic valve cusps were slightly stiffened. Atheromatous deposits and intimal ridges were also present in the aorta and common iliac arteries. The lungs appeared congested and edematous, and the right upper lobe was partially atelectatic. The spleen and liver showed chronic passive congestion.

The kidneys were both adherent to the surrounding connective tissue and to the posterior abdominal wall. They appeared similar, small and irregular in contour and uneven in consistency, varying from soft to hard. After fixation and removal of calculi they weighed about 50 gm. each (normal for the body length is about 95 gm. each). The capsule could be stripped only with extreme difficulty, leaving a pale reddish-mauve surface with many whitish-yellow raised hard calcareous flecks and plaques. On section, the kidney tissue was gritty, and its thickness was reduced to 0.2 to 0.8 cm. on the right and 0.6 to 1.0 cm. on the left (Fig. 5). The corticomedullary border was indistinct. On close inspection there were diffuse shimmering pinpoint deposits in addition to coarse flecks and plaques resembling those seen on the surface. The pelves and calyces were greatly dilated and contained numerous yellowish-brown calculi. The biggest on each side lay in the pelvis and was of staghorn type and was covered with some whitish deposit. The right pelvis was filled with whitish fluid containing purulent and sandy material; the left contained a smaller amount of similar material. The pelvic mucosa was thickened and congested, and the ureters were dilated to a diameter of 0.9 cm. on the right and 1 cm. on the left. They also contained calcareous-purulent material and their mucosa was congested; a brownish-yellow calculus of a diameter of 3 mm. was present in the lumen halfway down the left ureter. The bladder was small, and its mucosa was intensely congested and velvety. The internal ureteric orifices

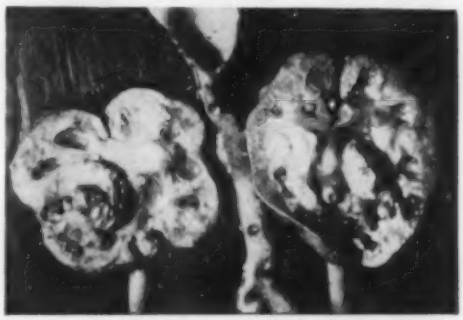


Fig. 5.—The kidneys show hydronephrosis, calculi in pelves and calyces, calcific flecks and plaques on the cut surface, and blurring of the corticomedullary border. The ureters are dilated. The abdominal aorta exhibits atheromatous changes.

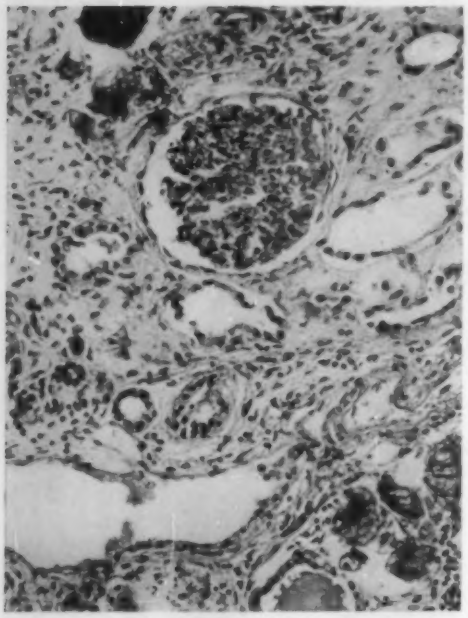


Fig. 5.—Kidney. The tubules are dilated and lined by flat or atrophic epithelium. An intact glomerulus is shown. Oxalate crystals are present in tubules and interstitial tissue. There is interstitial fibrosis and lymphocytic infiltration. Hematoxylin and eosin; reduced from mag. × 330.

were unusually wide, and the bladder neck showed some fresh submucosal hemorrhages.

The esophagus showed marked mucosal edema at its upper end and congestion with shallow erosions in its lowest part. The stomach was also congested and exhibited a few petechiae and three pinhead erosions. There was focal congestion in the small intestine, and the ascending colon contained mucosal hemorrhages. The larynx was somewhat edematous, and the trachea showed congestion and a few petechiae.

The two lower parathyoids were identified; the right weighed 26.2 mg. and the left, 37.4 mg.

The lumbar vertebrae on section showed rather a loose texture and soft consistency. Areas of softening were present along the centers of the posterior borders of the bodies. The right clavicle also had a slightly loose texture, and the marrow cavity was shimmering faintly. The right eighth rib exhibited two yellowish-white nodules of callus on its pleural surface. The ribs generally appeared unduly flexible. On section they showed irregular mottled yellowish, gray, and pink areas. The epiphyseal line was narrow and straight. The spinal cord and the remaining viscera appeared normal.

Postmortem x-ray examination of the kidneys showed fine streaky and speckled calcification of the parenchyma and heavy large shadows consistent with renal and pelvic stones. The lumbar vertebrae were demonstrated to be mineralized poorly in general but adequately in the provisional zone of calcification. The sternal end of the right eighth rib showed a fracture about 2 cm. from the end, with unusually dense internal and external callus.

Microscopic examination revealed most striking abnormalities in the kidneys and bones. The normal structure of the kidneys had been largely destroyed by a combination of extensive crystal deposition with acute and chronic pyelonephritis and some degree of calcification. In many areas glomeruli and tubules could still be seen. Here the glomeruli were evidently reduced in number, and the remaining ones mostly showed great thickening of Bowman's capsule, while hyalinization and vacuolation of the tuft were evident in some. The tubules exhibited degeneration, dilatation, and distortion, and many contained colorless or faintly greenish-yellow, doubly refractile crystalline deposits in the lumen, usually in the form of radiating segmented rods or broken plates (Figs. 6 and 7). Elsewhere, such crystals lay in rounded spaces lined by a basement membrane with only occasional fragmented epithelium and surrounded by necrotic structures. Other tubules contained hyaline casts, and some col-

Fig. 7.—Kidney. Rounded masses of crystals are deposited in tubules. The crystals are in the form of broken plates or sheaves of needles. A glomerulus is hyalinized. Ehrlich's acid hematoxylin; reduced from mag. × 330.

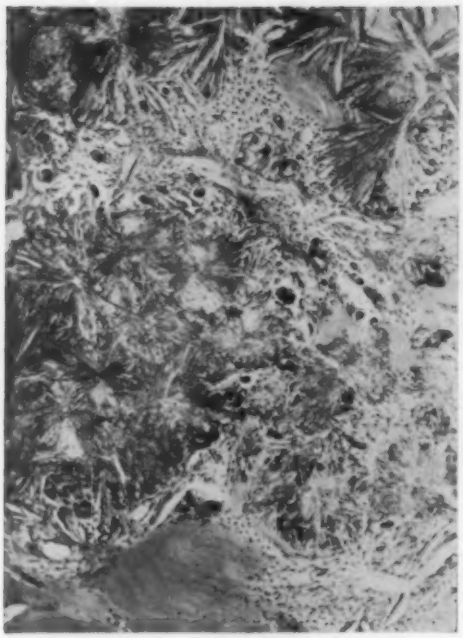


Fig. 8.—Clavicle. Rosettes of crystals are present in the marrow cavity. Fibrous tissue is seen around them, and many giant macrophages are in evidence. At the top right hand corner, crystals lie in a bony matrix without evident cellular reaction. Hematoxylin and eosin; reduced from mag. × 135.

lecting tubules were filled with necrotic material and polymorphonuclear cells. The arterioles showed intimal hypertrophy and degeneration, with thickening and folding of the internal elastic lamella; the adventitia was frequently continuous with an encircling sheath of connective tissue which was sharply demarcated from surrounding crystal spaces. The interstitial tissue showed some fibrosis and was diffusely and focally infiltrated with lymphocytes, mononuclear cells, and occasional polymorphonuclear cells. The pelvis was thickened and infiltrated with similar cells so that the structure of its epithelium was obscured. Large portions of renal parenchyma had been entirely replaced by a honeycomb network of rounded or oblong spaces containing rosettes of crystalline rods and needles. Each rosette was surrounded by a thin septum of connective tissue, in which fibroblasts, mononuclear cells, and multinucleate macrophages could be seen. In some areas the septa between these spaces had become calcified and, rarely, even bone formation had supervened. The capsule of the kidney exhibited fibrous thickening and leucocytic infiltration. Von Kossa stain showed the crystals as black, and cresyl violet stained them purple. Scarlet red stain demonstrated only a few scattered fat globules and droplets in degenerating renal cells, particularly in glomeruli.

In the sections of lumbar vertebra, clavicle, and rib the most striking finding was that the marrow cavity contained a large number of crystal deposits, which had replaced much of the marrow. Here the crystals were usually arranged in rosettes or sheaves of segmented rods and needles rather than as plates or rounded particles. They were generally surrounded by at least a few strands of fibrous tissue and appeared to excite a mild cellular reaction, with fibroblasts, mononuclear cells resembling osteoblasts, and giant cells morphologically identical with osteoclasts. The degree of reaction was, however, variable (Fig. 8). Sometimes new bone deposition had occurred in the vicinity. In some places, particularly when lying directly in bony matrix, the crystals had excited hardly any cellular response. Elsewhere, groups of crystal stars were embedded in sheets of fibrous tissue. It was notable that areas of intact marrow rarely contained such fibrous tissue (Fig. 9). Fibrosis without evidence of crystal deposition was observed in a few foci but not to the extent seen in true osteitis fibrosa. In several areas, particularly in the clavicle, the pattern of bony trabeculae was entirely lost and had been replaced by a honeycomb network of crystal deposits like that described in parts of the kidneys (Fig. 10).

Fig. 9.—Lumbar vertebra. This section shows fibrous tissue surrounding crystal deposits but absent from unaffected bone marrow. Hematoxylin and eosin; reduced from mag. × 135.

Fig. 10.—Lumbar vertebra. Honeycomb network of crystal rosettes in marrow cavity. Ehrlich's acid hematoxylin; reduced from mag. × 165.

Fig. 11.—Rib. Low-power view of crystals in polarized light. Hematoxylin and eosin; × 130.

The crystal rosettes formed a beautiful color pattern in polarized light (Figs. 11 and 12).

Endochondral bone formation in rib and vertebra appeared to be proceeding normally. The residual marrow was also normal. Cysts or osteoclastomata were not seen. The rib section included the fracture site, and there was little unaffected marrow left in this area. Along the inner aspect of the cortex there were some amorphous masses of necrotic bone, in which a few Gram-negative bacilli were demonstrated. The periosteum and new cortical bone over the fracture site were unusually thick.

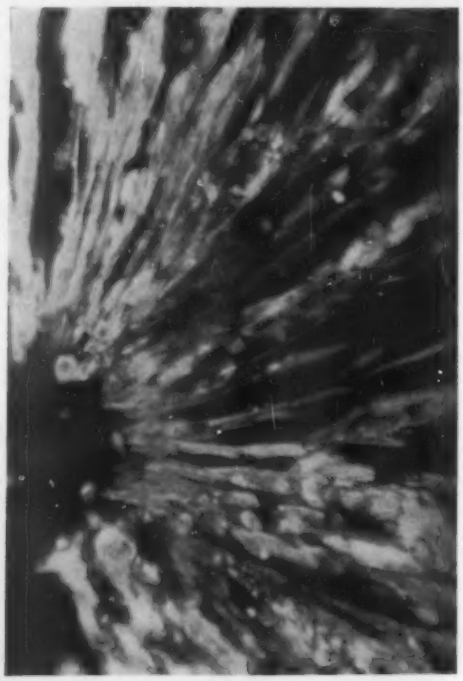


Fig. 12.—Rib. High-power view of crystals in polarized light. Hematoxylin and eosin; × 575.

Sections of the heart showed one rosette of crystals in the interstitial tissue adjacent to a small artery; slight hypertrophy of myocardial fibers, patchy thickening of the epicardium, and intimal hypertrophy and early atheromatous change in a coronary artery were also noted. The aorta and common iliac arteries exhibited fibrous intimal thickening with early atheroma, but there was no calcification. The lungs showed congestion, edema, and patchy atelectasis, and there was some focal bronchitis. In the spleen some central arterioles exhibited intimal hypertrophy, and congestion and hemosiderosis were evident. In the liver there was some excess of connective tissue in the portal spaces, and this extended into the perisinusoidal spaces,

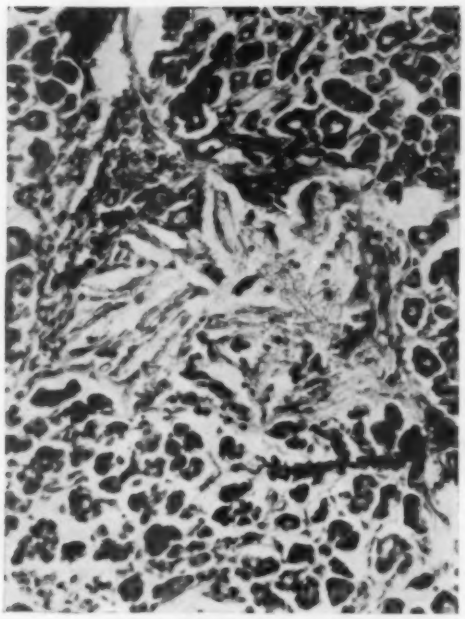


Fig. 13.—Pancreas. A cluster of crystals lies within the parenchyma. Hematoxylin and eosin; reduced from mag. × 330.

which were edematous; hemosiderosis and mild centrilobular atrophy were also present. The gall bladder was normal and contained no crystals. Section of the pancreas revealed two rounded spaces, each containing a rosette of rod-like birefringent crystals, with peripheral interdigitations of connective tissue containing macrophages (Fig. 13). The adrenals were normal. The bladder showed acute and chronic cystitis. The ovaries were somewhat fibrotic; numerous follicles were present, but none were seen near the surface or appeared to be ripening. The erosions in esophagus and stomach were demonstrated histologically, and vascular congestion was present in these organs and in the colon. The thyroid contained follicles of variable size, lined by low cuboidal epithelium and filled with abundant colloid; two interstitial spaces of average follicle size had birefringent crystals within them, chiefly sheaves of broad needles and broken plates, surrounded by strands of fibrous tissue and macrophages (Fig. 14); a few similar crystalline masses were seen in follicles, either free in the colloid or separated from it only by a layer of macrophages. Sections of the lower parathyroids were normal; the dark chief cells predominated, but some cells were slightly larger and paler, suggesting early transitional change; oxyphil cells were not seen. A perirenal lymph node showed acute lymphadenitis. A submandibular salivary gland and the spinal cord were normal on section.

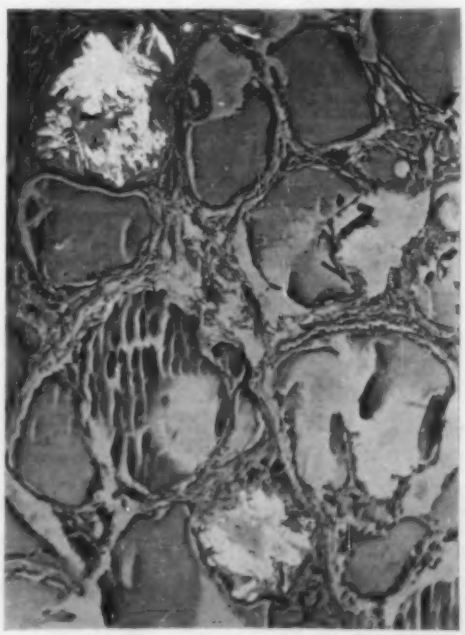
Chemical Examination.—Two renal calculi were examined chemically. They contained 18.6% and 10.6% of calcium, respectively, and also albumin or fibrin and gave positive tests for calcium and oxalate, but not for carbonates, phosphates, or ammonia. A piece of kidney tissue, preserved in 10% formaldehyde, was found to contain 59.4 mg. of calcium per gram wet weight.

Chemical tests were also performed on the crystals. They did not dissolve in dilute acetic acid, saturated ammonia, or 60% potassium hydroxide. They did dissolve in dilute hydrochloric acid after a few minutes. In strong potassium hydroxide they remained even when the surrounding tissue had been destroyed.

Further analysis of the crystals in the kidney tissue and bone marrow cavity was undertaken by Mr. William J. Cohen in Prof. Paul F. Kerr's laboratory, at the Department of Geology, Columbia University.

Optical examination showed that single-needle crystals averaged 0.05 mm. in length and 0.005 mm. in width. They had a birefringence of approximately 0.15 and an extinction angle of about 30 degrees with respect to the length of the crystal. The indices of refraction α and γ were 1.49 and 1.65 as determined by the immersion method. These data fit the optical properties of calcium oxalate monohydrate as reported by Prien and Frondel.[39]

Fig. 14.—Thyroid. Crystals are present in interstitial tissue and appear to lie in follicles. Hematoxylin and eosin; half-polarized light; reduced from mag. × 165.



Crystal fragments and plates had similar birefringence and refractive indices and could have arisen from breakage or different cleavage.

X-ray diffraction powder diagrams were obtained from the crystals in the clavicle. Again, the pattern was that of calcium oxalate monohydrate, and the figures were in good agreement with those reported by Prien and Frondel [39] and given in the A. S. T. M. Index.[40]

COMMENT

It is now possible to indicate some of the features of oxalosis as illustrated by the published cases and to discuss them in relation to the present patient. For the purposes of this discussion it is proposed to omit Laas' [32] patient, the 25-year old man, in whom renal oxalate deposits constituted a surprise finding at autopsy. We are then left with seven children with renal oxalosis, and a few of the main points are presented in the Table and in the following comments:

Cases of Renal Oxalate Deposits in Children

Reference	Country	Sex	Age at First Symptoms	Age at Death	Urinary Calculi	Urinary Infection	Extrarenal Oxalate Deposits
Lepoutre, 1925	France	?	? (Biopsy at 4½ yr.)	—	Present	?	.....
Vischer, 1947	Switzerland	M	10 yr. 7 mo.	11 yr.	Absent	? Absent	None noted
Davis and others, 1950	U. S. A.	M	2 yr. 8 mo.	12 yr.	Present	Mostly absent	In bones
Mulloy and Knutti, 1951	U. S. A.	M	4 mo.	5 mo.	Absent	Absent	None noted
Ying Chou and Donohue, 1952	Canada	M	1 yr. 11 mo.	6 yr. 11 mo.	Present	Present	In bones; slight in heart, lungs, thymus, spleen, and pituitary
Newns and Black, 1953	Great Britain	F	2 yr.	—	Present	Absent	.....
Present case	U. S. A.	F	? 4 yr.	15 yr. 10 mo.	Present	Present	In bones; slight in heart, pancreas, and thyroid

Sex Incidence.—Of the six children in whom the sex has been recorded, only two were girls. The higher incidence in males in this small series may perhaps be related to the well-known fact that renal calculi generally occur predominantly in males, not only in adults but also in children.†

Age Incidence.—All these patients were children. As far as is known, they appeared healthy at birth and developed satisfactorily in the neonatal period. The age at which symptoms attributable to oxalosis commenced varied from 4 months in the case of Mulloy and Knutti [35] to over 10½ years in Vischer's [33] patient. In the former, the course of the disease was acute and ended in death within a month, while in the girl now presented the course of the disease lasted nearly 12 years. Renal failure was always the direct or indirect cause of death, but the rate at which it progresses appears to vary considerably in this disease.

Heredity.—It is interesting that the elder brother of the patient of Newns and Black [36] had died of renal failure with oxalate nephrolithiasis and that in Ying Chou and Donohue's [30] case and in the present one the father had passed a urinary stone of unknown type. It is known that calcium oxalate stones may sometimes be passed by several members of a family,‡ and it seems quite likely that renal oxalosis and oxalate stone formation are related abnormalities. In the family recorded by Gram [43] the tendency to form oxalic urinary calculi appeared to be inherited dominantly but showed itself practically only in male members. If heredity plays a part in the etiology of oxalosis, the mode of inheritance may again be at least partially dominant, for only one parent had passed urinary calculi in any one case and consanguinity of the parents, commonly observed in recessive conditions, has not so far been recorded in this disease.

Dietary History.—None of the children reported so far had any history of having taken abnormal diets and, in particular, foods with a high oxalate content. The boy recorded by

† References 41 and 42.

‡ References 43 and 44.

Davis and colleagues [34] as well as the present patient had a high milk consumption, and the infant reported by Mulloy and Knutti [35] had hardly progressed beyond milk feedings. Milk is known to reduce the absorption of oxalic acid by converting it to insoluble calcium oxalate in the gastrointestinal tract,§ and so milk would in fact tend to counteract a high oxalate intake in the diet. The possibility of a high consumption of foods, such as carbohydrates, which Loeper || calls "oxaligenic" because they may give rise to oxalates during metabolism, is more difficult to eliminate but is not supported by the available dietary details.

Clinical Manifestations.—The main symptoms in the terminal phase of the disease were always those of renal failure, such as thirst, polyuria, fatigue, drowsiness, loss of appetite, vomiting, shortness of breath, tetany, and hemorrhages. These need not be detailed here, though it may be pointed out that two of six children with an adequate history had convulsions and a third had recurrent hemiparesis. Sometimes symptoms of renal failure are the first manifestation of the condition, and this would seem to be the rule whenever the renal oxalate deposits are unaccompanied by urinary calculi. Such calculi were present in only five of the seven recorded cases. When present they are liable to cause colics, hematuria, or dysuria early in the disease, and there may be obvious passage of stones or gravel. Further, they may be responsible for the maintenance of urinary infection with its consequent symptoms, such as frequency of micturition, dysuria, pyuria, abdominal pain, and fever. However, only two of the five children with calculi in this series had infected urine. In this connection it may be remembered that the majority of patients with calcium oxalate stones are free of urinary infection.¶

The physical findings may be normal in the early phase or may be confined to the signs produced by urinary calculi, sometimes accompanied by infection. Later, the signs of renal failure, with its association of uremia, acidosis, tetany, and cardiac insufficiency, will supervene. It is perhaps noteworthy that our patient is so far the only one who is known to have been markedly dwarfed and underweight. Davis and colleagues [34] even emphasize that the boy they describe showed excellent growth and development until the terminal stage. One wonders whether the marked and persistent infection and consequent pyelonephritis were partly responsible for the stunted growth in the present case.

An interesting symptom common to Davis' [34] patient and ours was the pain and stiffness in the legs. In both children this occurred during their last year of life. It was associated with muscle tenderness and spasm and with hyperactive deep tendon reflexes and thus could be attributed to tetany. However, in the present case there also appeared to be tenderness of the underlying bones with deep-seated pain, and this might be due to the morphological changes in the bones like the bone pains of hyperparathyroidism.

The pathological fractures which occurred in our patient have not been previously described in oxalosis. They are evidently a late symptom due to severe bone changes.

Radiological Findings.—Scattered fine opacities throughout the renal parenchyma are a characteristic finding in oxalosis and were already present in the infant who died at 5 months. This disease thus has to be considered whenever "nephrocalcinosis" is demonstrated radiologically. In addition, radiopaque calculi may be present in the urinary tract, and sometimes a characteristic structure with radiating spicules indicates that they consist of calcium oxalate. The secondary effects of stones, such as hydronephrosis and dilatation of ureters, may be shown by pyelography, and intravenous pyelograms may also indicate impaired excretion of the contrast agent.

X-ray examination of the long bones did not reveal any abnormality in two recorded cases.# In our patient it showed widespread

§ References 14 and 45.

|| References 8 and 9.

¶ References 46 and 47.

References 35 and 36.

changes during her final years. These changes were highly suggestive of osteitis fibrosa cystica and included such striking features as *Umbauzonen,* subperiosteal rarefaction, and invisibility of the dental lamina dura.

Laboratory Investigations.—In all the adequately documented cases the urine contained albumin, varying from a trace to 3+, and exhibited leucocytes in the deposit. Red cells were also frequently present. As mentioned, bacteria may or may not be demonstrable. Surprisingly, calcium oxalate crystals were found in the urine in only two of these children * but they may well have been overlooked, particularly in the presence of many leucocytes in the deposit, as in our case. The urinary calcium excretion was measured in four of these children, including the present one, and was found to be within normal limits, or even somewhat low, whether by quantitative estimation of the daily output or merely by application of the Sulkowitch test to single specimens.

The changes in blood chemistry reflect the renal insufficiency in the later stages of the disease and need not be discussed in detail. It is noteworthy that the serum alkaline phosphatase was within normal limits in the three previous cases in whom it was estimated and on no fewer than 12 occasions in the present patient.

Blood studies revealed a severe anemia in most of these children during the stage of marked renal insufficiency. This anemia was generally normochromic or moderately hypochromic. Both Davis' [34] patient and our own required so many transfusions during their final year that one is tempted to attribute the anemia not only to renal failure but also to the replacement of bone marrow by oxalate crystals.

In future cases, two further types of investigation could be of interest and of help in diagnosis. First, bone marrow aspiration may reveal the presence of calcium oxalate crystals, analogous to the finding of cystine crystals in cystinosis. Secondly, oxalate levels in blood and urine might be determined, if a satisfactory technique can be evolved.† Such investigations were carried out by Newns and Black [36]; they were unsuccessful in searching for crystals in marrow smears, but they demonstrated an increased urinary oxalate excretion in their patient.

Pathology.—The serous effusions and cardiac hypertrophy found in our patient are presumably associated with renal failure; they have been described in a previous case [34] and need not detain us here. The main interest centers on the lesions in the kidneys themselves. Here the cardinal feature is the deposition of calcium oxalate crystals in the tubules, and the basic histological picture has been well described in experimental animals suffering from chronic oxalate poisoning.‡ Crystals, which are birefringent and usually colorless but sometimes yellowish, tend to fill the lumina of the renal tubules. The shape of the crystals varies from spherical forms, often with radial striation, to dumbbells and wedge-like aggregates of needles. The epithelium of the tubules in which the crystals are situated is often compressed and may be atrophic, with thickening of the basement membrane. Scanty small foci of round cells are present in the interstitial tissue, which is also edematous. The glomeruli are generally unaffected.

This basic picture appears to have been present in fairly pure form in the infant with renal oxalosis described by Mulloy and Knutti,[25] though the authors add that in some areas the tubule structure seemed to have disappeared and an increase of interstitial tissue was noted about crystalline material. In the boy who died at nearly 7 years [30] tubular atrophy was extensive, and in addition to the changes just described slight thickening of the glomerular basement membranes and condensation of renal parenchyma with slight interstitial fibrosis were noted. In the children who died after the age of 10 years the kidneys had become more fibrotic and disorganized. They were now smaller than normal (*Schrumpfniere*); the

* References 30 and 36.

† References 20-22, 48, and 49.

‡ References 24 and 26.

tubules were distorted and frequently dilated, and the glomeruli were reduced in number and exhibited hyalinization and fibrosis of the tufts and thickening of Bowman's capsule without definite crescent formation, while the interstitial tissue was fibrotic. This appearance may be complicated by pyelonephritis owing to infection, as in the present case. Finally, extensive areas of the kidney may become entirely replaced by a honeycomb network of crystal deposits with fibrous septa. Foci of calcification, staining bluish with hematoxylin, may also appear as in Davis' [34] patient and in ours; these presumably represent the "dystrophic calcification" which is not uncommon in chronic pyelonephritis (see Vaughan and co-workers [50]).

Bones are the other site, apart from the kidneys, where extensive deposits of calcium oxalate crystals are found, and one may speculate whether this is due to the presence of large numbers of calcium ions, which could assist in the precipitation of oxalate. The crystals are deposited within the marrow spaces and also in bony trabeculae, and they tend to be more in the shape of sheaves and rosettes of segmented needles and rods than in spherical or dumb-bell forms. There is great variability in the degree of tissue reaction; in some areas the crystals may lie in bone with hardly any evidence of cellular reaction, while elsewhere they may stimulate not only osteoblastic and osteoclastic activity but also the production of fibrous tissue. The marrow may be largely replaced by crystal deposits, which often form a honeycomb network as described in the kidney.

Isolated rosettes or clusters of crystals in other tissues were present in the case described by Ying Chou and Donohue [30] as well as in ours, particularly in the myocardium and endocrine glands.

Calcium oxalate crystals, whatever their shape, always show a high degree of birefringence.[39] They can be identified by chemical and optical tests. In addition, x-ray diffraction methods were used in the case of the infant [35] and in the present patient. In both these children calcium oxalate was shown to be in the monohydrate form, which is also the commonest component of oxalate calculi.

The crystals do not take up the routine stains generally used. Ebstein and Nicolaier [27] found that they that could be stained by using Ehrlich's acid hematoxlyin, while Laas [32] noted that they appeared reddish when exposed to cresyl violet. In our case the latter method proved the more successful; the crystals, however, stained purple rather than red. Three previous groups of authors § made the puzzling observation that the crystals were not shown up by the von Kossa method of staining, generally used for calcium salts. On the other hand, the isolated group of oxalate crystals described by Glynn [24] and the deposits in our patient were strongly positive to von Kossa stain. It is true [38] that this method does not stain calcium per se, but only certain salts, such as phosphates. However, Cameron [51] who carefully investigated von Kossa's test, found that calcium oxalate reacted very strongly and was only equaled by the phosphate in its intensity of staining.

The Problem of Hyperparathyroidism.—The presence of renal calculi, when combined with radiological changes indicative of generalized osteitis fibrosa cystica, as in our case, is liable to suggest a diagnosis of hyperparathyroidism. In that condition the stones usually consist of calcium phosphate, but they may occasionally be composed of calcium oxalate,[37] and so the diagnosis is not invalidated by finding the latter component.

In the series of cases here analyzed there was never any surgical or autopsy evidence of a primary parathyroid tumor. However, secondary renal hyperparathyroidism is more difficult to eliminate. The features which might indicate its presence are the radiological bone changes in the present case and the weight and structure of the parathyroids in several of these patients. Pappenheimer and Wilens [52] found that lower parathyroid glands of normal adults weighed about 31 to 32 mg. each, and so our patient, who died at less than 16 years of age and was mark-

§ References 30, 34, and 35.

edly dwarfed, had lower parathyroids of adult weight. Again, the two parathyroids identified in the case of Ying Chou and Donohue [30] together weighed 46.7 mg., which is approximately equivalent to the normal total of all four glands in that child's age group, while the four parathyroids in Davis' [24] patient had a total weight of 188 mg., or twice the normal for that child's age (see Gilmour and Martin [58]). Also, in two cases in this series there was histological evidence of hyperplasia of the parathyroid.‖

There is, however, strong evidence against any marked degree of hyperparathyroidism in these cases. First, the histology of the parathyroids was normal in the patient of Ying Chou and Donohue,[30] and in ours any of the histological abnormalities described by Gilmour [54] were carefully excluded. Secondly, the pathological changes in the present patient's bones did not conform to those of osteitis fibrosa cystica; in particular, the fibrosis of the marrow was generally restricted to areas of crystal deposition. Thirdly, the blood chemical findings did not indicate hyperparathyroidism, and the normal alkaline phosphatase in our case is a particularly strong argument against parathyroid overactivity as a cause of the bone disease.[55] Fourthly, the normal or low urinary calcium excretion in several of these patients argues against any notable hyperparathyroidism. Finally, there was never any clinical or autopsy evidence of metastatic calcification in soft tissues other than the kidneys.

ETIOLOGY

It has been suggested [30] that oxalosis is the result of an inborn error of metabolism in which oxalic acid is formed in excessive amounts and combines with calcium to form a relatively inert compound. This is certainly more likely than that it should represent a defect in calcium metabolism, for hypercalcemia and hypercalciuria were absent in the reported cases and animal experiments show that the prevalence of monohydrate forms of calcium oxalate in the urine indicates a relative preponderance of oxalate over calcium ions.[16] However, the disturbance in oxalic acid metabolism which is probably present in these patients is still unproved. It is known that in the case of urinary oxalate stones there is no definite correlation between the degree of oxaluria and calculus formation (see Jeghers and Murphy [12]), and a deficiency of substances keeping oxalate in solution may be the decisive factor.¶ Such a deficiency of protective electrolytes or colloids is perhaps less likely to account for widespread systemic precipitation of calcium oxalate, but it must be considered as a possible etiological mechanism in oxalosis.

Most authors consider that oxalic acid cannot be further broken down in human tissues #; therefore, its increased concentration in blood and urine could be accounted for only by excessive absorption or endogenous formation. In the recorded cases of oxalosis there has been no evidence of a high dietary oxalate intake; consequently, a metabolic derangement would have to be postulated. The metabolic origin of oxalates is a confused and controversial subject, of which Jeghers and Murphy [12] wrote an execellent summary in 1945. Only a brief outline will be given here. First, Loeper and his colleagues * have long maintained that, in addition to preformed oxalate, food may contain metabolic precursors of oxalate; in his terminology, the diet may be not only "oxalophoric" but also "oxaligenic." He considers that the most "oxaligenic" foodstuffs are carbohydrates, especially glycogen and starches, and there is some experimental evidence in favor of this view.† Secondly, it has been shown that intestinal bacteria and parasites, for instance, Taenia,[9] can produce oxalic acid. Thirdly, oxalate is evidently an end-product of tissue metabolism, but its exact derivation here is still obscure and requires a short discussion.

‖ References 34 and 35.

¶ References 16, 17, 56 (cited by Jeghers and Murphy [12]), and 57.

References 16 and 21.

* References 8 and 9.

† References 14 and 58.

The French school has long claimed that endogenous oxalates are chiefly derived from the intermediary metabolism of carbohydrates. It has been demonstrated that oxalic acid may arise from glycogen in tissue slices [8] and from glucose in blood.[59] Hyperoxalemia is said to accompany hyperglycemia in diabetes mellitus,[8] though this observation has not been universally confirmed.[14] Insulin has been found to reduce the urinary output of oxalate in animals, while pancreatectomy has the opposite effect.[60] However, recent biochemical studies have thrown little light on any pathway by which oxalate could be derived from carbohydrates. Although oxalacetic and oxalosuccinic acid take part in the Krebs citric acid cycle for the breakdown of pyruvate, there appears to be no evidence that oxalic acid itself can be formed from these compounds in the tissues.

Lately, evidence has accumulated that oxalic acid may be formed in the metabolic breakdown of ascorbic acid. This had been suspected on the basis of experiments in vitro [61] and in guinea pigs [62] and was then demonstrated by the use of radioactive carbon in these animals. Burns, Burch, and King [63] found that 0.6% to 3.24% of the C^{14} administered to guinea pigs in the form of ascorbic acid reappeared in the urine incorporated into calcium oxalate. The formation of oxalate from glucose was also confirmed by these authors but appeared quantitatively insignificant by comparison. In man, recent studies showed that the ingestion of large amounts of ascorbic acid increased the urinary excretion of oxalic acid significantly.[64]

Oxalic acid is $(COOH)_2$. Some of the simple chemical substances with a similar formula, ethylene glycol $(CH_2OH)_2$, for example,‡ have been shown to be converted into oxalic acid in the body. Creatinine and aminoacetic acid (glycine) are among the more important physiological substances in this group, and their possible role as metabolic precursors of oxalate has been a controversial subject in the literature. In the case of aminoacetic acid, CH_2NH_2COOH, enzymes promoting its oxidative deamination to glyoxylic acid, CHO.COOH, and the oxidation of the latter to oxalic acid have been demonstrated in various animal tissues, particularly in the kidneys.[66] However, aminoacetic acid is glycogenic while oxalic acid is not, and it is clear that aminoacetic acid must be metabolized largely through other pathways. The discovery of the interconvertibility of aminoacetic acid and serine[67] provided one alternative route for aminoacetic acid utilization. Further, recent isotope studies in the intact rat showed that of a variety of 2-carbon acids, including aminoacetic acid, only glyoxylate gave a high yield of oxalate and that all acids except oxalate were readily oxidized to carbon dioxide.[68] It may be concluded that aminoacetic acid is not an important metabolic precursor of oxalate.

Finally, it is possible that oxalic acid may be an end-product of pyrimidine metabolism via oxaluric acid, $NH_2.CO.NH.CO.COOH$.[69] This substance occurs in traces in normal human urine and yields oxalic acid and urea on hydrolysis. However, a recent review does not include oxaluric and oxalic acid as recognized end-products of pyrimidine breakdown in man.[70]

It must be emphasized that normal urine is supersaturated with calcium oxalate [17] and that increased concentration does not necessarily result in precipitation. Among the electrolytes which increase its solubility magnesium is reported to be the most important.[16] Vitamins A and D also help to prevent precipitation,[16] and urea, colloids, and certain acids may exert a protective role.[46] Whether similar substances are required to prevent precipitation in the tissues does not appear to have been explored.

From a pediatric point of view, it is of interest that in a series of children the level of oxalic acid in the blood tended to be highest in infancy and to diminish progressively with increasing age, reaching adult values at puberty.[71] This higher blood level may be conducive to the precipitation of calcium oxalate in the tissues of young children.

‡ References 29 and 65.

TREATMENT

Most of the instances of oxalosis so far recorded were diagnosed after death. In future it should be possible to make the diagnosis in life, and the question of treatment will arise. In view of our ignorance concerning the underlying metabolic defect, therapy will have to be based largely on past experience and experiments with oxalate calculi and on the few known facts about oxalate metabolism.

The diet should, of course, avoid all food with a high oxalate content, and it may be advisable to give milk freely, as this tends to convert oxalic acid into insoluble calcium oxalate and thus to prevent its absorption. Alkalis also impair the absorption of oxalates,[19] and alkalosis is said to lead to a fall in the level of oxalic acid in the blood. According to Albright and colleagues,[37] citrate will not redissolve urinary oxalate stones but may hinder their precipitation. On the other hand, acids have been used to increase the solubility of calcium oxalate in the urine; this effect, however, is only attained if the pH of the urine is kept below 5.[16] It is probably more important to increase this solubility by administering electrolytes, for instance, in the form of a saline solution containing certain amounts of calcium, magnesium, and phosphate (Hammarsten's mixture).[17] An adequate fluid intake should be assured, and Burkland [46] advises patients with oxalate calculi to drink 8 to 10 glasses of water daily. Vitamins A and D should be given in sufficient amounts.

Restriction of calcium in the diet has been found to lead to a paradoxical increase in the urinary excretion of calcium in animal experiments [58] and is inadvisable. More reasonably it may be argued that the diet should be low in carbohydrates and should contain only the essential minimum of vitamin C, as these substances may be broken down to oxalic acid in their catabolism. Adequate daily exercise and the elimination of indigestion and constipation have also been advised.[46] The most recent therapy for the prevention of urinary oxalate calculi appears to be the subcutaneous administration of hyaluronidase,§ but this must still be considered as of doubtful value.

There is general agreement in the literature that medical treatment is more successful in preventing the formation of urinary oxalate concretions than in dissolving them. Once stones are formed, their surgical removal may be required, and the successful treatment of any accompanying urinary infection often depends on the prior removal of the calculi.

SUMMARY

More than a century ago the concept of an "oxalic acid diathesis" was established, a metabolic disorder manifested by a variety of neurasthenic, dyspeptic, and rheumatic symptoms and by the passage of calcium oxalate crystals in the urine. The concept of such a syndrome, now often called "oxalemia," still lingers in Continental Europe, but it has fallen into disrepute in the English-speaking countries. The biochemical data supporting it are technically unreliable, and a pathological basis has never been established.

Evidence from experimental chronic oxalate poisoning in animals would lead one to expect that a disease in which oxalic acid accumulates in the body would cause calcium oxalate deposits in the renal tubules. Such deposits have never been demonstrated in persons alleged to suffer from "oxalemia" but have recently been encountered in a different kind of patient, namely, in a few children who died of renal failure, often after passing oxalate calculi in the urine. Two of these children were also demonstrated to have extensive deposits of calcium oxalate in bones, and one had a few clusters of such crystals in various viscera. The condition has been named oxalosis.

Another such case is reported. The patient was a girl who first had hematuria at the age of 4 years and who was found to have a urinary infection and bilateral hydronephrosis with multiple renal and ureteric calculi at 5 years. Her renal function gradually became impaired. At 13 years she suffered

§ References 72-74.

two fractures after slight trauma, and x-ray examination showed generalized osteoporosis with osteitis fibrosa cystica, as well as nephrocalcinosis and nephrolithiasis. Neck exploration was performed, and the parathyroids were found to be normal. She finally died from renal failure at the age of 15 years and 10 months. At autopsy, the renal pelves and calyces were full of calculi consisting of calcium oxalate with an admixture of protein. The renal parenchyma showed extensive deposits of crystalline material as well as pyelonephritis and focal calcifications. Large deposits of similar crystals were found in the bones, and a few clusters were present in the myocardium, pancreas, and thyroid. On analysis by chemical, optical and x-ray diffraction methods, the crystals were demonstrated to consist of calcium oxalate monohydrate.

It appears most logical to assume that this child had a primary disturbance of oxalate metabolism which led to the deposition of calcium oxalate in the kidneys and other tissues and to the formation of renal oxalate stones and that the latter in turn were responsible for the maintenance of urinary infection.

The features of oxalosis are discussed in the light of this and previously published cases. The sex and age incidence, heredity, dietary history, clinical manifestations, radiological and laboratory findings, and pathology are reviewed. The etiology at present is hypothetical; overproduction of endogenous oxalic acid would appear to be the most likely cause, but a possible derangement of substances which normally keep oxalate in solution must also be considered. Some of the facts and theories concerning oxalate metabolism are briefly quoted, and the possible treatment of oxalosis is indicated.

Dr. Ruth C. Harris gave advice and performed many chemical investigations in the case here described; Dr. Dorothy H. Andersen gave guidance in the interpretation of autopsy findings; Prof. Paul F. Kerr and Mr. William J. Cohen investigated the crystals in the patient's tissues; Dr. John Caffey gave help in interpreting the x-ray films, and Dr. Rustin McIntosh gave encouragement and criticism.

ADDENUM

Since this article was submitted for publication a few further reports of the disease in the recent literature have come to my attention. Ostry [75] described two patients with nephrocalcinosis, and the first of these evidently suffered from oxalosis. This was a man, 24 years of age, who died of renal failure three years after his first attack of hematuria; autopsy showed calcium oxalate calculi and crystals in the kidneys. Zollinger and Rosenmund [76] made a careful study of the pathology in three patients with renal oxalate deposits. The first was a man, aged 35, the second a diabetic woman of 57, and the third a boy of 4½ years. All three had died of renal failure. The boy was the only one who also had oxalate deposits in bones; further, he exhibited agenesis of one kidney and Klippel-Feil syndrome of the cervical spine as associated congenital defects. Aponte and Fetter [77] reported three cases of oxalate nephrocalcinosis occurring in one family. They were all boys, and the first two were identical twins. Death was due to renal failure at 16, 13½, and 9 years, respectively. The twins had a 24-hour urinary oxalate excretion of 200 and 180 mg.; both also had oxalate deposits in vertebral bone marrow at autopsy. It is interesting that all three boys had high serum uric acid levels. There were three healthy siblings, two of them female. Finally, Burke and his colleagues [78] published the case of a boy who died of the disease at 11 years 10 months, having first had hematuria at the age of 3 years. This patient had deposits of calcium oxalate in bones, liver, spleen, and adrenal cortex and in the walls of arterioles as well as in the kidneys.

The predominance of the condition in males is further shown by these reports, and the sex incidence in the recorded cases now totals 11 males to 3 females. It is apparent that the condition may occur in adults, but oxalate deposits in bone marrow have not yet been demonstrated in these. The present

need is for cases to be diagnosed in life so that biochemical studies of the metabolic error can be undertaken. The elucidation of this rare disorder may contribute to the better understanding of the commoner, and probably related, problem of oxalate stone formation in the kidneys.

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PHEOCHROMOCYTOMA IN CHILDREN

Report of Case

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THERE ARE many causes of hypertension in children, one of the most interesting and rarest of which is chromaffin tumor of the adrenal medulla, usually called "pheochromocytoma," or chromaffinoma of extra-adrenal chromaffin tissue, termed "paraganglioma."

Pheochromocytoma is rare in adults and rarer still in children. However, over the past 10 years there has been an increasing number of cases reported in children. This increase seems to be largely due to the development and use of pharmacologic tests, especially the histamine test,* the piperoxan (benzodioxan) test,† and the phentolamine (Regitine) test.‡ Most authorities agree that these tests are highly reliable and very useful in establishing a diagnosis of pheochromocytoma.

The purpose of this paper is to report a case of pheochromocytoma in a child and to review the literature on pheochromocytoma in children.

REPORT OF CASE

A 12-year-old white boy, admitted to the Mayo Clinic on March 5, 1954, had complained of headaches located in the temporal region for about five months. His illness had begun in October, 1953, and was manifested by headache which occurred about once weekly at any hour of the day or night and which often followed physical exertion. At that time there were no other complaints associated with the headache. About three and one-half months after the onset, epistaxis occurred. Initially the epistaxis followed blowing of the nose, but as the headaches became more severe, it would occur without apparent provocation. The family physician advised hospitalization.

On admission to the local hospital the patient had a systolic blood pressure of 250 mm. of Hg and a diastolic pressure of 160 mm. During hospitalization he had a generalized clonic convulsion which was followed by a semistuporous condition that lasted for 48 hours. Later there were two episodes of vomiting that lasted 12 to 24 hours each. All examinations and special tests conducted at that time failed to reveal the exact cause of the hypertension. However, it was thought that the hypertension was malignant in nature. The patient was dismissed after two weeks in the hospital and was advised to take medication to stabilize the blood pressure.

For the next four weeks the patient continued to have recurrences of headache and vomiting. These had increased in severity and occurred during the day or night at intervals of about three or four days. During this period there was loss of appetite and a weight loss of 24 lb.

On the evening of the day of admission to the Mayo Clinic the child complained to his mother that he felt drowsy and very tired, and his mother noted that he was unable to walk. He was, therefore, admitted to the hospital for care and study. He complained of headache and of feeling very warm.

The family history was not significant. Growth and development of the patient had been normal. Physical examination revealed a well-developed well-nourished white boy who was restless and agitated. The blood pressure was 220 mm. of Hg systolic and 150 mm. diastolic. The pulse rate was 90 beats per minute, the temperature was 98 F, and the respiratory rate was 22 per minute. The pupils were dilated, but both reacted to light and accommodation. Funduscopic examination revealed a bilateral papilledema of 2 D. and variable narrowing of the arterioles without evidence of chronic sclerosis. Occasional spastic constrictions were noted. Hemorrhage was apparent at the superior nasal portion of the left disk (Fig. 1*a*). These findings were interpreted as representing an active angiospastic episode, probably the result of pheochromocytoma. The ears, nose, throat, chest, heart, and lungs were normal. There was no splenomegaly or

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* References 1 and 2.

† References 1 and 3-7.

‡ References 6 and 8-10.

hepatomegaly. All reflexes were normal, and no pathologic reflexes were elicited.

The specific gravity of five specimens of urine ranged from 1.009 to 1.015. There was also albuminuria, Grade 1 to 3. Microscopic examination gave negative results. The number of erythrocytes and leucocytes, the value for hemoglobin, and the differential count were normal. The value for blood urea was 22 mg. and for serum sulfate 4.3 mg. per 100 cc. The zinc sulfate test for hepatic function gave a value of 9 units. A roentgenogram of the chest, a roentgenogram of the kidneys, ureters, and bladder, an excretory urogram, and an electrocardiogram revealed no abnormalities. The basal metabolic rate was +9. A tuberculin reaction was negative.

The blood pressure was recorded every four hours (Fig. 2). On both the second and third hospital days as well as on the evening of admission, the patient had episodes of acute anxiety, was very restless, complained of feeling warm, and his hands were cold and clammy. The systolic and diastolic blood-pressure readings at these times, respectively, were 234/170, 210/146, and 230/160. These episodes plus the ophthalmoscopic manifestations indicated the need for one of the chemical diagnostic tests for pheochromocytoma.

On the fifth hospital day the first test with phentolamine was done. Five milligrams of the drug was given intravenously. The blood pressure dropped from the preinjection level of 200/154 to 120/88 within 30 seconds after injection of the drug (Fig. 3). A second phentolamine test was done the following day with only 3.5 mg. of the drug. The results were similar to those of the previous test; the blood pressure dropped from the preinjection level of 204/150 to 150/124 within 30 seconds (Fig. 4). The diagnosis of pheochromocytoma was definitely made.

At the time of operation a tumor was removed from the left adrenal gland. Exploration of the abdomen failed to reveal the presence of any other chromaffin tumors. The tumor was a pheochromocytoma. It weighed 20 gm. and measured $4 \times 3 \times 3$ cm. It was encapsulated and well differentiated. Microscopic examination showed clusters of typical cells with abundant granular cytoplasm (Fig. 5), and chemical analysis revealed a norepinephrine content of 2.0 mg. per gram of tumor and an epinephrine content of 0.5 mg. per gram.

Throughout the surgical procedure and for the first 48 hours postoperatively the patient was under constant observation. The blood pressure ranged from 100/70 to 110/80 during the first four hours postoperatively (Fig. 6). Throughout the next 24 hours it ranged from 100/70 to 116/80, and for the following 24 hours from 90/60 to 124/80. The course was uneventful, and the blood pressure stabilized at 120/80.

Nine days postoperatively the patient underwent cold pressor and histamine tests. The blood pressure changed from 116/78 to 154/116 during the cold pressor test. After intravenous injection of 0.025 mg. of histamine the blood pressure rose from 120/80 to 140/94. The responses to these tests were within the range of normal and constituted further evidence of the absence of other chromaffin tumors.

Reexamination by the ophthalmologist on the tenth postoperative day revealed narrowing of the arterioles, Grade 2, no focal constrictions, bilateral papilledema about Grade 2—, no hemorrhagic areas,

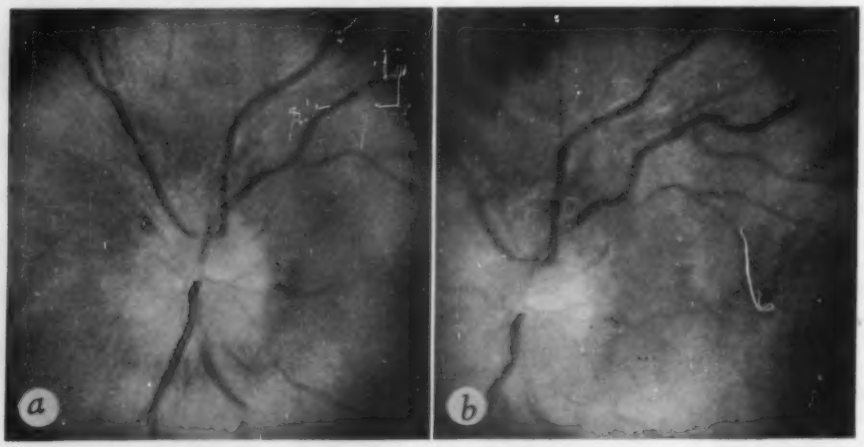

Fig. 1.—Fundus of the left eye. (*a*) Prior to operation. Note arteriolar narrowing, papilledema, and an area of hemorrhage at the superior nasal portion of the disk. (*b*) Ten days postoperatively. Note changes in arteriolar constrictions, absence of hemorrhagic area, and residue of edema at the superior pole of the disk.

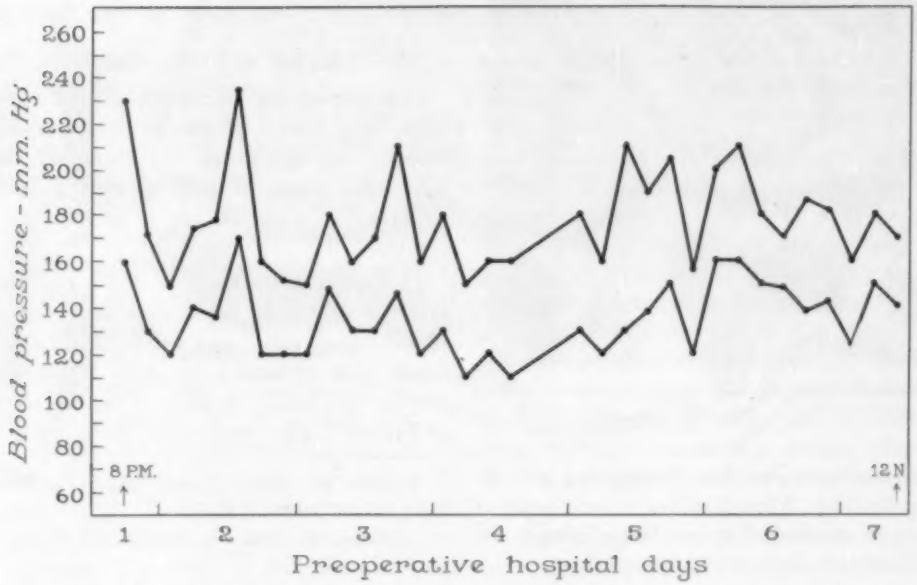

Fig. 2.—Recordings of blood pressure prior to operation. Note peaks of blood pressure, coinciding with acute anxiety episodes, on admission and on the second and third hospital days.

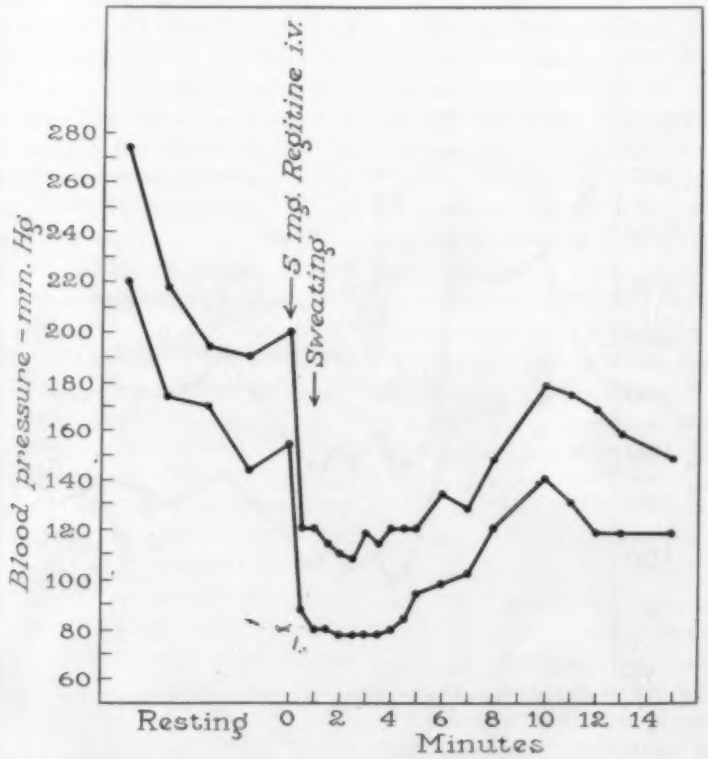

Fig. 3.—Recordings of blood pressure during the first test with 5 mg. of phentolamine given intravenously. There is a sudden sharp drop in blood pressure.

and evidence of residue of edema at the superior pole of the left disk (Fig. 1*b*). The blood pressure at the time of dismissal was 134/90.

This is the first case of pheochromocytoma in the pediatric age to be reported from this clinic. It is of interest and importance for several reasons. It demonstrates that funduscopic examination is helpful in establishing the diagnosis of pheochromocytoma. Close observation of the patient is necessary, and in this case revealed the occurrence of characteristic paroxysmal hypertensive episodes which are often seen in patients with chromaffin tumors. The corroborative evidence obtained with the phentolamine test is to be emphasized. Though pheochromocytoma is rare in children, it should be included in the differential diagnosis of hypertension.

REVIEW OF LITERATURE

In reviewing the literature we found a few interesting reports which do not represent cases in our age group but which will be mentioned briefly because of their general importance to the subject of pheochromocytoma.

Howard and Barker,[11] in 1937, reported that the first clear description of a case of pheochromocytoma was made by Labbe, Tinel, and Doumer § in 1922. However, Snyder and Vick,[12] in 1947, noted the work of Fränkel ‖ also, reported in 1886, in which

§ Labbe, M.; Tinel, J., and Doumer, cited by Howard and Barker,[11] p. 372.

‖ Fränkel, F., cited by Snyder and Vick, [12] p. 594.

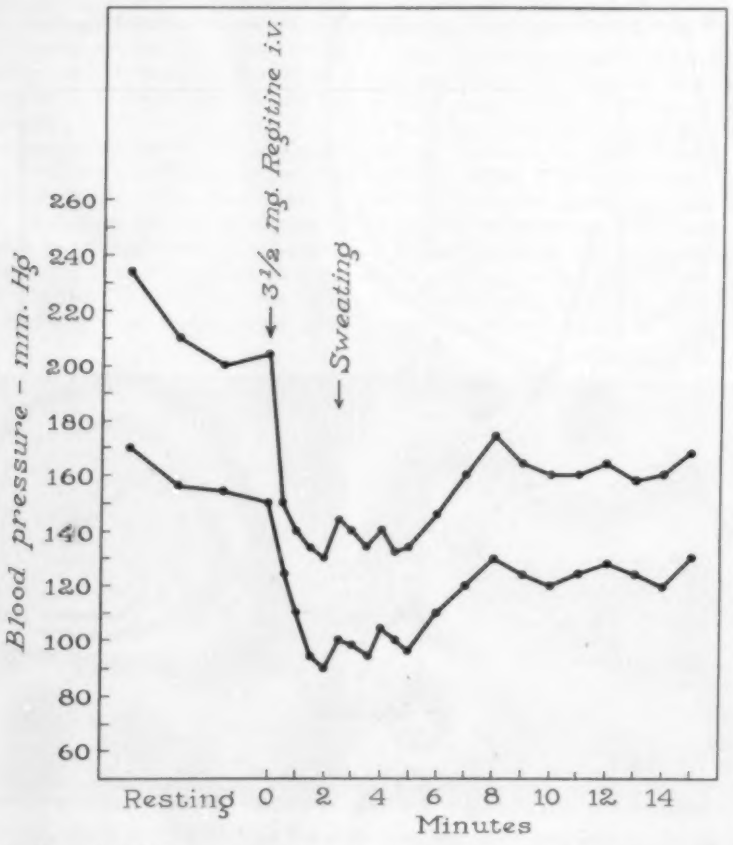

Fig. 4.—Record of blood pressure during second phentolamine test with 3.5 mg. of the drug given intravenously. The curves in Figures 3 and 4 are similar.

he accurately described the syndrome of paroxysmal hypertension.

In 1927, C. H. Mayo [13] reported the first removal of a tumor originally noted as a retroperitoneal malignant blastoma. Later, reexamination of the tumor by Rowntree and Ball [14] revealed it to be a pheochromocytoma.

The combination of correct preoperative diagnosis and successful surgical treatment in a case of pheochromocytoma was accomplished by Shipley,[15] in 1929.

Concerning children, Snyder and Vick,[12] in 1947, reviewed all the proved cases of pheochromocytoma with special attention to those that occurred in patients less than 13 years of age. They cited four previous cases and presented three of their own. They also mentioned the case of von Neusser and Wiesel,¶ in which an adrenal medullary chromaffin tumor in a 2-year-old infant was found at necropsy.

Since 1947 several authors # have reviewed the literature on pheochromocytoma in children. Because of the arbitrary age limitation set by various authors, the total number of cases has varied from report to report. We selected the age of 14 years in order to include previous work on the subject in children.

The previously reported cases are summarized in the Table. The clinical picture presented by these patients has been reported by several authors.* In the case reported by Yu and Shan,[29] operation was refused, and the diagnosis was based upon roentgenologic examination of the renal areas. Another case, reported by Koffler and co-workers,[1] was not included in the Table because the patient was 15 years of age when the diagnosis of pheochromocytoma was made; however, this patient had been under observation from the age of 12 years for persistent hypertension, and at the age of 15 years the correct diagnosis was made, with the aid of the piperoxan test, and a right adrenal tumor was removed at operation.

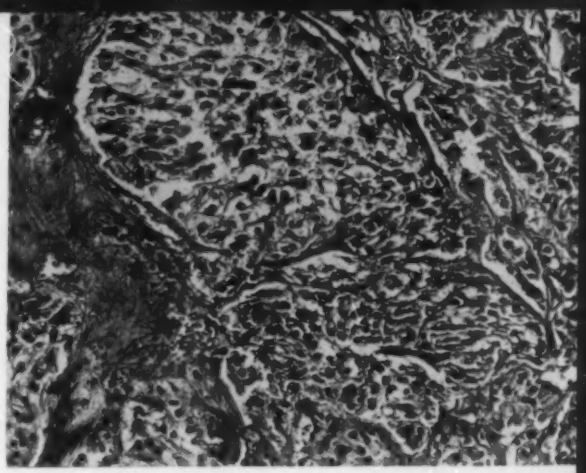

Fig. 5.—Section of tumor tissue showing clusters of typical cells with abundant granular cytoplasm (hematoxylin and eosin; × 140).

The data presented in the Table may be summarized as follows. The total number of reported cases of pheochromocytoma in children aged 14 years or less is 28. The ratio of whites to nonwhites is 7 : 2. The ratio of boys to girls is 2 : 1.

The sites of occurrence of the tumors were as follows: extra-adrenal, nine cases; left adrenal, eight; both adrenals, eight, and right adrenal, six. These total more than 28 cases because in 3 of the patients with a tumor in the left adrenal, tumors were also found in extra-adrenal sites, and in 1 case of bilateral adrenal involvement there was also an extra-adrenal tumor.

Operation was performed on 18 patients. Eight died during or after the operation, and 10 recovered and remained well. In view of the extremely poor prognosis for patients with untreated pheochromocytoma, the operation is indicated in all cases.

SUMMARY

A case of pheochromocytoma in the left adrenal gland of a 12-year-old white boy is reported. The diagnosis was made by clinical observation, funduscopic examination, and repeated phentolamine (Regitine) tests. Treatment was surgical and resulted in cure.

Reports of 27 cases of pheochromocytoma in patients aged 14 years or less have been published previously. The present report is

¶ von Neusser, E., and Wiesel, J., cited by Snyder and Vick,[12] p. 593.

References 7 and 16-19.

* References 9, 11, 12, 25, and 29.

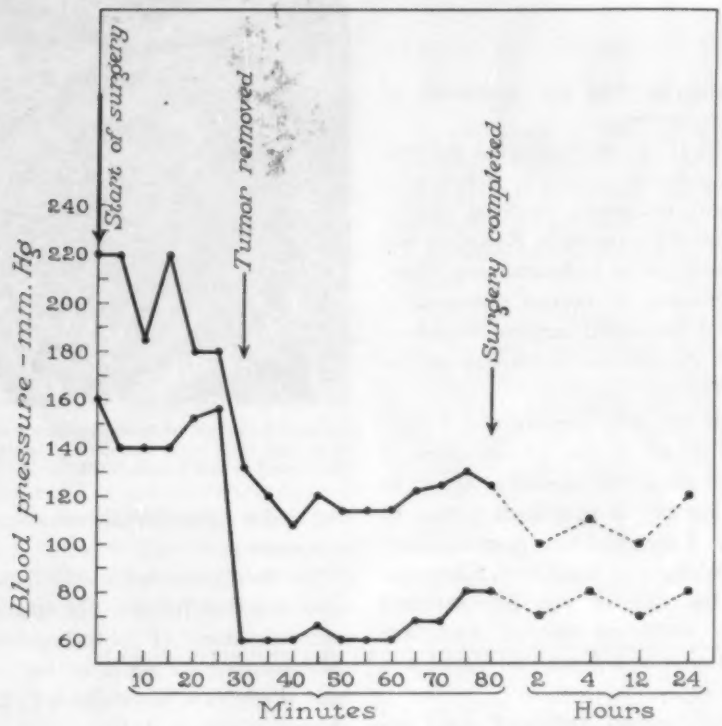

Fig. 6.—Record of blood pressure during and immediately after operation. Note change on removal of tumor.

Reported Cases of Pheochromocytoma in Children Aged Fourteen Years or Less

Year	Author	Age, Yr.	Sex	Race	Site of Tumor	Operation *
1910	von Neusser and Wiesel †	2	..	...	.....	.....
1936	Kremer [20]	14	F	W	Bilateral	None
1937	Evans [21]	12	F	W	Left adrenal, tail of pancreas	None
1941	Knake [22]	11	M	W	Bilateral	Yes; D
1942	Neff and co-workers [23]	1½	F	W	Left adrenal	Yes; L
	Linneweh ‡	10	M	W	Bilateral	Yes; D
	Evans and Stewart [24]	14	F	N	Right adrenal	Yes; L
1946	Espersen and Dahl-Iversen §	10	M	W	Mass in front of large vessels, continuous with left adrenal	Yes; D
1947	Snyder and Vick [12]	11	M	W	Right adrenal	Yes; D
		12	F	W	Left adrenal and mass mesial to left adrenal	Yes; L
		11	F	N	Right side near aortic bifurcation and filling foramen of Winslow	Yes; D
1948	Cahill [8]	10	F	W	Between aorta and vena cava in Zuckerkandl body	Yes; D
		11	M	W	Mesial to hilus of right kidney	Yes; L
1949	Litman and State [19]	11	F	W	Right adrenal	Yes; L
	Grimson and co-workers [9]	10	M	N	Right adrenal	Yes; L
1950	McCoy and Bridgeman [7]	13	M	W	Left adrenal	Yes; L
1951	Bastrup-Madsen [16]	9	F	W	Left adrenal	None
	Iseri and co-workers [10]	8	M	N	Medial to lower pole of left kidney	Yes; L
	Hubble [18]	11½	M	W	Bilateral and aortic glands	Yes; D
	Soffer and Gabrilove [25] ‖	7	M	W	Extra-adrenal	None
1952	Neill and Smith [26]	6	M	W	Bilateral	None
	Talbot and co-workers [27] ¶	6	M	W	Bilateral	Yes; D
1953	Klein and co-workers [28]	11	M	W	Left adrenal	None
	Goldfarb [17]	9	M	N	Bilateral	None
	Yu and Shan [29]	14	M	Y	Right side (presumably in right adrenal)	None
1954	Schaefer and co-workers [30]	10	M	W	Bilateral	None
	Isralelski and co-workers [31]	10	M	W	Right adrenal	Yes; L
	Smid and DuShane	12	M	W	Left adrenal	Yes; L

* L, living postoperatively; D, died during or soon after operation.
† von Neusser, E., and Wiesel, J., cited by Snyder and Vick,[12] p. 593.
‡ Linneweh, F., cited by Snyder and Vick,[12] p. 593.
§ Espersen, T., and Dahl-Iversen, E., cited by Snyder and Vick,[12] p. 592.
‖ No data given as to operation.
¶ Case of Dr. S. Farber but used by Talbot and associates in their textbook.

the 28th. Of 18 patients treated surgically, 10 recovered and 8 died.

Pheochromocytoma should be considered in the differential diagnosis of hypertension in children.

ADDENDUM

Since this paper was submitted for publication, four additional reports of pheochromocytoma in children under the age of 14 years have appeared in the literature. Popper and Theron [32] reported the successful surgical removal of a right adrenal tumor in a 13-year-old Bantu boy. Daeschner and coworkers [33] reported a case in a 4-year-old white boy, and Snyder and Rutledge [34] reported one in a 13-year-old white boy; in each instance a right adrenal tumor was removed surgically. In Case 3 reported by Lukemeyer,[35] a pheochromocytoma of the right adrenal gland was removed successfully in a 7-year-old white boy.

These cases bring to 32 the total number of reported cases of pheochromocytoma in children aged 14 years or less. Because of the fact that a good surgical result was obtained in all four of the added cases, the incidence of such results in the expanded series of 32 cases was appreciably higher than in the original series of 28 cases.

Dr. Grace M. Roth supervised and directed the phentolamine tests, Dr. R. W. Hollenhorst gave assistance and the use of his photographs of the fundi, Dr. E. V. Allen gave consultations, and Dr. J. T. Priestley performed the operation.

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Abstracts from Current Literature

Anatomy and Physiology

IMMUNIZATION OF INFANTS WITH TRIPLE ANTIGEN. G. V. FELDMAN, Arch. Dis. Childhood **29**:175 (June) 1954.

In a series of more than 200 infants, antibody response to all three constituents of a triple antigen was satisfactory in those tested.

The reactions were no more severe than those following single antigens.

Because the addition of tetanus does not interfere with the production of diphtheria and pertussis antibodies, its inclusion is a useful addition to the routine protection of children.

KELLY, Milwaukee.

SOME ASPECTS OF FOETAL AND PLACENTAL PHYSIOLOGY. W. F. WIDDAS, Études néo-natal. **3**:165 (Sept.) 1954.

The relationship between fetal weight and conception age is discussed. The cube root of weight plotted against age is reasonably linear during the latter half or two-thirds of pregnancy and is a useful representation in laboratory mammals. It may be of value in estimating the age of human fetuses.

Some recent work on the fetal circulation as studied in the sheep has been reviewed. Experiments on this animal are helpful in advancing our detailed knowledge of the changes which occur in the circulation at birth. One example is the finding (Dawes and co-workers, 1953) that expansion of the lungs by air lowers the pulmonary vascular resistance and increases the pulmonary blood flow.

In addition to the grosser changes at birth, physiological study reveals many examples of smaller and more subtle changes or contrasts between the intrauterine fetus and the postnatal animal. In the sheep these are exemplified by the sugar fructose, by *m*-inositol, and by changes in the rate of water penetration into the erythrocytes.

Fetal erythrocytes in several species of mammals are permeable to sugars, whereas the adult erythrocytes are negligibly so. In the human adult the erythrocytes are permeable to sugars, but the cells of fetal blood are more permeable. Since the transfer of sugars is by a carrier transfer, differences in permeability are evidence of some change in the surface biochemistry of the cells themselves.

Although these examples of changing biochemistry and cell physiology studied in experimental mammals may not have immediate application to clinical neonatal and prematurity problems, they call for a greater awareness of the fact that in changing from the intrauterine to the early postnatal existence, with the severance of the influence of the placenta, there are fairly abrupt changes, both biochemical and physiological, at the cellular level.

FROM THE AUTHOR'S SUMMARY.

Metabolism; Infant Feeding; Milk and Other Foods

C^{14} STUDIES IN CARBOHYDRATE METABOLISM: I. THE OXIDATION OF GLUCOSE IN NORMAL HUMAN SUBJECTS. N. BAKER, W. W. SHREEVE, R. A. SHIPLEY, G. E. INCEFY, and M. MILLER, J. Biol. Chem. **211**:575 (Dec.) 1954.

This paper describes the techniques employed in an effort to elucidate some aspects of carbohydrate metabolism in living man. To this purpose glucose labelled with radioactive carbon was administered to four adult subjects and the fate of the glucose determined by studies of blood and expired air. Expressions for the size of the active glucose pool of the body and the rate at which glucose is converted to CO_2 were obtained.

This report is illustrative of the attempts of modern scientists to apply tracer methodology to the study of complex metabolic functions in the living subject.

FORBES, Rochester, N. Y.

FREE AMINO ACIDS OF CHICK CHORIO-ALLANTOIC MEMBRANES AND THE INFLUENCE OF VIRUS INFECTION. C. A. JOHNSON, J. E. KEMPF, and O. BERGEIM, J. Biol. Chem. **211**:757 (Dec.) 1954.

Studies in 14- and 15-day-old chick embryos were carried out in order to determine what effect, if any, virus infection may have on the amino acid content of the embryonic host. Fourteen amino acids were studied.

A definite decrease in histidine, lysine, arginine, and serine levels occurred as a result of infection with influenza A virus. No change resulted from infection with mumps virus.

FORBES, Rochester, N. Y.

THE AMINO ACID REQUIREMENTS OF MAN: VII. GENERAL PROCEDURES; THE TRYPTOPHAN REQUIREMENT. W. C. ROSE, G. F. LAMBERT, and M. J. COON, J. Biol. Chem. **211**:815 (Dec.) 1954.

This paper reviews the work of the author over a period of years in which the requirement of young men for tryptophan was studied. Nitrogen balance was maintained on a diet containing 0.15-0.25 gm. of *l*-tryptophan daily, and the author concludes that 0.25 gm. is the minimal daily requirement.

It is of interest that, in contrast to some other mammalian species, man utilizes *d*-tryptophan to a very slight extent, if at all.

FORBES, Rochester, N. Y.

THE FREE AMINO ACIDS OF HUMAN BLOOD PLASMA. W. H. STEIN and S. MOORE, J. Biol. Chem. **211**:915 (Dec.) 1954.

Using column chromatography, the authors were able to identify 28 ninhydrin-positive substances in protein-free plasma and to determine most of them quantitatively. Values are given for 21 amino acids in postabsorptive adult plasma.

In one patient with cystinuria, the cystine, arginine, and alanine contents were slightly reduced while that of glycine was elevated. In another, with phenylpyruvic oligophrenia, phenylalanine content was markedly increased while the other amino acids were at the normal level.

FORBES, Rochester, N. Y.

THE AMINO ACID REQUIREMENTS OF MAN: VIII. THE METABOLIC AVAILABILITY OF THE OPTICAL ISOMERS OF ACETYLTRYPTOPHAN. W. C. ROSE, M. J. COON, and G. F. LAMBERT, J. Biol. Chem. **212**:201 (Jan.) 1955.

Studies of young adult men, using the nitrogen balance technique, revealed that acetyl-*l*-tryptophan was utilized fully as well as the parent compound, but that acetyl-*d*-tryptophan was not utilized to a significant extent. The acetyl forms of both isomers behave in man much as the parent compounds.

These findings stand in contrast to those noted by others for the rat, since this species can utilize both acetyl and free forms of the *l*-isomer and the free form of the *d*-isomer, but fails to utilize acetyl-*d*-tryptophan for growth.

FORBES, Rochester, N. Y.

NUTRITIVE VALUE OF THE DIETS OF IOWA SCHOOL CHILDREN. ERCEL S. EPPRIGHT, VIRGINIA D. SIDWELL, and PEARL P. SWANSON, J. Nutrition **54**:371 (Nov. 10) 1954.

This paper reports the average daily nutrient intakes of a sample of Iowa school children classified by sex and by age in years consecutively from 6 to 18. A total of 1188 children were studied. Mean daily intakes of food energy and 10 nutrients have been estimated from seven-day dietary records. Except for calcium, boys tended to have larger mean intakes of food energy and nutrients at successive years. The intakes of girls of 6 to 12 years tended to increase irregularly, but beyond 12 years food-energy and nutrient consumption remained the same or decreased, except for ascorbic acid. Nutrient intake of girls changed markedly at 12 years, and at 16 years negative deviations from the allowances were especially noticeable. Except in calcium, the mean daily nutritive value of the diets of boys at most ages and of girls 6 through 12 years approximated or exceeded the National Research Council Recommended Allowances. Girls tended to have diets below the allowances in most nutrients after 12 years of age; the deviations were greatest in iron and calcium. In each age-sex group approximately 12%, 42%,

and 46% of the total food-energy value of the diet was obtained from protein, fat, and carbohydrate, respectively. Mean daily protein intake during school age decreased from 2.7 to 1.1 gm. per kilogram of body weight for girls; 2.9 to 1.5 gm. for boys.

FREDEEN, Kansas City, Mo.

STUDIES IN CALCIUM METABOLISM: EFFECT OF FOOD PHYTATES ON CALCIUM^{45} UPTAKE IN CHILDREN ON LOW-CALCIUM BREAKFASTS. FELIX BRONNER, ROBERT S. HARRIS, CONSTANTINE J. MALETSKOS, and CLEMENS E. BENDA, J. Nutrition **54**:523 (Dec. 10) 1954.

In the investigation reported by Felix Bronner and co-workers, radioactive calcium (Ca^{45}) was used to study the effect of phytates (inositol hexaphosphates) on the uptake and excretion of calcium in a group of adolescent boys. Nineteen adolescent boys, of inadequate intelligence but otherwise normal, who were institutionalized in a state school under uniform nutritional and environmental conditions volunteered for these experiments. In the present investigation the effect of a phytate-rich cereal (oatmeal) on the uptake of calcium was compared with that of phytate-free cereal (farina). Milk was used as the principal source of calcium. The effect of food phytates was further compared with that of soluble sodium phytate which was added to farina. In order to neutrilize any effects due to the solids content of the food, all meals were equalized to a common solids content by the addition of farina.

The data presented would lead to the conclusion that less calcium was taken up when sodium phytate or when a phytate-containing cereal was fed than when the phytate-free farina was ingested. These findings leave little room for doubt that phytate does interfere with calcium uptake and that less calcium enters the body when phytate-containing cereals are eaten. On the other hand, the absolute quantity of calcium rendered unavailable as a result of the action of the food phytate was so small that phytates cannot be very significant in the usual U. S. diets. The uptake of Ca^{45} by the boys on the oatmeal breakfast was 74% as great as that of the boys on the farina breakfast. The uptake of Ca^{45} by the boys on the farina plus phytate meal was 45% that of farina meal. Less Ca^{45} was taken up in the presence of sodium phytate than in the presence of an equivalent quantity of phytic phosphorus supplied by oats.

FREDEEN, Kansas City, Mo.

Vitamins; Avitaminoses

A RAPID, SIMPLE METHOD FOR THE DETERMINATION OF REDUCED, DEHYDRO- AND TOTAL ASCORBIC ACID IN BIOLOGICAL MATERIAL. R. R. SCHAFFERT and G. R. KINGSLEY, J. Biol. Chem. **212**:59 (Jan.) 1955.

This report presents a modification of the well-known 2,4-dinitrophenylhydrazine method for the determination of ascorbic acid. The method is less time-consuming than previous ones. Total ascorbic acid can be partitioned into the reduced and dehydro- forms rather easily.

Normal values for adult blood and urine and for a limited number of fruits and vegetables are given.

One disadvantage, as far as the pediatrician is concerned, is that the method calls for 5 ml. of blood.

FORBES, Rochester, N. Y.

HYPERVITAMINOSIS A: CLINICAL AND EXPERIMENTAL STUDIES. C. ZUNIN and F. TESTA, Minerva pediat. **6**:683 (Sept. 15) 1954.

Experiments with rabbits and guinea pigs indicate that hypervitaminosis A will result in abortion or premature birth. A chart for the differential diagnosis of hypervitaminosis and periosteal polyosteopathy (Caffey's disease) is given.

HIGGINS, Boston.

EXCESSIVE VITAMIN D ADMINISTRATION IN INFANTS AND PRESCHOOL CHILDREN. E. GRUNDLER, Deutsche med. Wchnschr. **80**:285 (Feb. 25) 1955.

Clinically excessive doses of Vigantol produced a picture characterized by neuropathic manifestations, lack of appetite, and constipation. The presence in urine of white and red blood corpuscles, cylinders, and sometimes calcium salts indicate a renal lesion. A hypercalcemia, 10.9 to 15.5 mg. per 100 cc., was present in 5 of the 10 cases observed, of which only the severest one is given in detail. The hypercalcemia appears as the latest manifestation.

AMBERG, Rochester, Minn.

Hygiene; Growth and Nutrition; Public Health

PHYSICAL MEASUREMENTS OF IOWA SCHOOL CHILDREN. ERCEL S. EPPRIGHT and VIRGINIA D. SIDWELL, J. Nutrition **54**:543 (Dec. 10) 1954.

The present study was planned by Ercel S. Eppright and Virginia D. Sidwell to reveal certain aspects of the physical growth of a state-wide sample of Iowa school children about whom considerable information concerning food habits, nutrient intake, and nutritional status was available. The present study presents means and standard deviations of five body measurements (weight, height, leg girth, hip width [biiliac diameter], and chest breadth) of approximately 1200 children ranging in age from 6 to 18 years. The means at successive ages, 6 through 18 years, agreed closely with norms based on a partially longitudinal study of Iowa City children. Mean weights at most ages tended to be larger, but mean heights were about the same as those observed in a mass study conducted in Iowa about 10 years ago. Thus a trend toward relatively greater gains in weight than in height was noted. By most standards of comparison fewer girls than boys were in the so-called normal range. At the age of 12, fewest children were within the normal range. Major differences in mean body measurements of children of successive ages were compared with mean nutrient intake. In teen-age children, mean weights and heights of girls tended to increase, although mean nutrient consumption apparently failed to increase or in some cases actually decreased with age. The diminishing calcium intake and the low levels of dietary iron of girls, whose growth has evidently not ceased, suggested the possibility of a poor quality of growth for girls during the teens.

FREDEEN, Kansas City, Mo.

RELATIONSHIP OF ESTIMATED NUTRIENT INTAKES OF IOWA SCHOOL CHILDREN TO PHYSICAL AND BIOCHEMICAL MEASUREMENTS. ERCEL S. EPPRIGHT, CHARLOTTE RODERUCK, VIRGINIA D. SIDWELL, and PEARL P. SWANSON, J. Nutrition **54**:557 (Dec. 10) 1954.

The purpose of the present analysis by Eppright and co-workers was to find out whether differences in level of nutrient intake were associated with differences in body measurements and nutritional status among the children themselves in the state-wide sample of Iowa school children. Furthermore, in view of the frequency with which the Recommended Allowances of the National Research Council are used in the evaluation of diets of groups of children, it seemed important to find out whether the children whose diets conformed fully to the allowances differed from those whose diets were lacking in at least one respect. Relationships between levels of nutrient intake of groups of school children and their development as revealed by body measurements, hemoglobin concentrations in blood, and serum concentrations of alkaline phosphatase, ascorbic acid, and carotenoids have been studied. Children with the liberal diets which conformed fully to the allowances tended to be slightly taller, heavier, and larger in leg girth than the children with diets at the other extreme, which on the average were somewhat below the allowances. No significant differences in hemoglobin or serum alkaline phosphatase concentrations were noted. The mean serum concentrations of ascorbic acid and carotenoids reflected the intakes of these two substances by the two groups of children, but other influences on the serum concentrations were evident. Age-sex differences in the serum concentrations of these two substances were noted among the children with liberal intakes. The differences in nutritional status of children noted in this study were small, but they are indicative of trends which need to be scrutinized for the large groups of children whose diets are not drastically poor but may be suboptional in nutrient content. The significance of these differences to the long-time health and well-being of children should be assessed through longitudinal studies.

FREDEEN, Kansas City, Mo.

THE EFFECT OF THE ADMINISTRATION OF METHYL ANDROSTENDIOL ON GROWTH. SALVATORE CORBO, Riv. clin. pediat. **54**:256 (Oct.) 1954.

The authors checked weight, height, and thoracic perimeter of 30 children (15 boys and 15 girls) 18 months to 3 years old; then they treated half of them with "metilandrostendiol" suppositories of 10 mg. each administered every day (except on Sunday).

Such treatment was carried out in two periods of 50 and 15 days, respectively, with an interval of 25 days between. In the treated children there resulted a weight gain of 7410 gm.,

that is, 3430 gm. higher than in a former period of the same duration. In the controls the weight gain was nearly the same in both periods. Height and thoracic perimeter of treated children showed a clinically significative increase too. FROM THE AUTHOR'S SUMMARY.

ASSESSMENT OF VARIOUS FACTORS IN GROWTH. J. F. DE WIJN, Maandschr. kindergeneesk. **22**:418 (Dec.) 1954.

In continuation of a previous paper dealing with various methods for the assessment of growth with the aid of standards, a general review is given of the main factors governing the growth and development of children.

Secular changes, environmental influences and climate, the socioeconomic milieu, illness, weight at birth, racial factors, psychic influences, and educational neglect are among the factors dealt with in relation to child growth. FROM THE AUTHOR'S SUMMARY.

Newborn

ERYTHROBLASTOSIS FETALIS: IX. THE PROBLEMS OF STILLBIRTH. FRED H. ALLEN JR., LOUIS K. DIAMOND, and A. RICHARDSON JONES, New England J. Med. **251**:443 (Sept. 16) 1954.

Stillbirth is a major problem in erythroblastosis caused by Rh incompatibility, since about 20% of the fetuses in these cases die in utero.

The authors observed 469 erythroblastic babies born to sensitized Rh-negative women in the Boston Lying-in Hospital. Stillbirths averaged 23% in this series.

High maternal titer and an unfavorable previous history influenced the outcome adversely. For example, when the titer was 1:256 or higher and a previous baby had died, 69% were stillborn.

With an unfavorable past history, more than one-half of the current stillbirths occurred before 33 weeks' gestation. The authors restate the belief that miscarriages before about 16 weeks are not caused by Rh sensitization and that anemia is the primary cause of intrauterine death, since it produces heart failure.

At present, delivery before term is the only known method of reducing the frequency of erythroblastic stillbirth late in pregnancy. This maneuver should be used only in selected cases, with due consideration of its temporal limitations and the ever-present hazards of prematurity. Exchange transfusions should be a prompt adjunct in therapy.

There is no evidence that cortisone or other drugs have any value in preventing stillbirths due to Rh incompatibility. WHEELOCK, Washington, D.C.

NON-SURGICAL TREATMENT OF UNILOBAR OBSTRUCTIVE EMPHYSEMA OF THE NEWBORN. HERBERT W. KORNGOLD and JOHN M. BAKER, Pediatrics **14**:296 (Oct.) 1954.

The reported 22 cases of unilobar obstructive emphysema in infancy are reviewed. Eighteen of these cases were successfully treated by lobectomy or segmental resection. No cause of the obstruction was found in over 50% of the cases reported.

Two cases of unilobar obstructive emphysema in the newborn are presented. These patients were successfully treated by selectively decompressing the emphysematous lobe.

The nonsurgical method of treatment is advocated in the newborn when lobar emphysema is newly established and reversible. It may be of value when surgery is indicated to improve the patient who is a poor risk.

The mechanism by which selective decompression alleviates the partially obstructed bronchus is open to conjecture. However, we postulate that the bronchus is kinked by an overdistended emphysematous lobe and that retained viscid secretions augment the bronchial obstruction in the newborn infant. FROM THE AUTHORS' SUMMARY.

ABNORMALITIES OBSERVED DURING THE FIRST SIX DAYS OF LIFE IN 8,716 LIVE-BORN INFANTS. LLOYD E. HARRIS and ARTHUR G. STEINBERG, Pediatrics **14**:314 (Oct.) 1954.

This is a report of the abnormalities, both congenital and acquired, observed during the first six days of life in 8,716 liveborn infants. Postmortem findings are not included. The difficulties encountered in reporting and comparing the incidence and frequencies of abnormalities

are discussed, the methods of gathering the data are described, and terms are defined when necessary. The abnormalities are presented according to systems, namely, gastrointestinal, respiratory, nervous, genitourinary, skeletomuscular, blood and cardiovascular, and skin.

FROM THE AUTHORS' SUMMARY.

Chronic Infectious Diseases

RESPONSE TO BCG VACCINATION AS AN INDEX OF FAMILIAL SUSCEPTIBILITY TO TUBERCULOSIS. SVEN NISSEN MEYER and CARROLL E. PALMER, Am. Rev. Tuberc. **69**:383 (March) 1954.

Previous work has suggested that there is a familial variation in susceptibility or resistance to tuberculosis. Similarly, reactions to tuberculin as well as local lesions after BCG variation have shown a familial pattern (size of the lesions). This study attempted to relate familial resistance or susceptibility to the type and degree of response to BCG vaccination.

A simple relationship between the two could not be established by statistical analysis of the data. It was found that the combination of small local lesions and high allergy suggested greater familial resistance than the inverse combination, and that a rapid development of local lesions may also be associated with resistance.

ROYCE, Pasadena, Calif.

THE VITAL CAPACITY AS A MEASURE OF THE SPONTANEOUS BREATHING ABILITY IN POLIOMYELITIS. B. G. FERRIS JR., A. WARREN, and C. A. BEALS, New England J. Med. **252**:621 (April 14) 1955.

The vital capacity is a useful index of the need for respiratory aid during the course of poliomyelitis. Expressed as a percentage of the predicted vital capacity, it can be used as an index to determine when a patient should be given a trial in a tank respirator and to guide the weaning program. It is recommended that when the vital capacity falls below half the predicted value, the patient should be given a trial in a respirator. The beneficial implications of this are discussed. Furthermore, when the vital capacity is below a third of the predicted value, use of a tank respirator during several hours of the day is indicated. The exact length of time tank respirators or other devices will be required will vary, depending on individual considerations.

FROM THE AUTHORS' SUMMARY.

A LATE EVALUATION OF PATIENTS WHO HAD TUBERCULOSIS WHEN UNDER TWO YEARS OF AGE. B. RONDININI, Clin. pediat. **36**:439 (June) 1954.

Of a group of 126 children who had tuberculosis when they were under 2 years of age, between 1937 and 1947, 45% had died and 71% had had family exposure. Thirty-five of the children were examined 9 to 15 years later clinically and by x-ray. Only two of this group showed new tuberculosis processes. Each of the others showed recovery of the childhood lesions.

It would appear that the early tuberculous infection had in these cases afforded a valuable protection against reinfection.

HIGGINS, Boston.

THE VIRULENCE OF STRAINS OF THE TUBERCLE BACILLI AS RELATED TO THEIR SUSCEPTIBILITY TO STREPTOMYCIN. G. CASCIO and R. PURPURA, Minerva pediat. **6**:597 (Aug. 15) 1954.

Guinea pigs inoculated with strains of tubercle bacilli which had been found very susceptible to streptomycin in vitro lived longer than guinea pigs which had been inoculated with less susceptible strains.

HIGGINS, Boston.

THE DEVELOPMENT OF SIGNS OF INTOLERANCE TO ISONIAZID IN A GIRL OF EIGHT YEARS. C. SALAMONE, Minerva pediat. **6**:600 (Aug. 15) 1954.

An 8-year-old girl with primary pulmonary tuberculosis had been treated with streptomycin and paraaminosalicylic acid for several weeks. Then isoniazid was given for six days with beneficial results in that the temperature had returned to normal. On the seventh day, 40 minutes after taking isoniazid, she had a severe chill with fever, reddening of the skin, vomiting, and diarrhea. Five days later the medication was again tried, and once more the child became very

sick with fever, gastrointestinal disturbances, and urticaria. A third trial was made some time later, this time with another drug company's product, but the same reaction occurred. This time, there was an enlargement of the liver and the Takata-Ara test proved positive.

HIGGINS, Boston.

TREATMENT OF OXYURIASIS IN CHILDHOOD. WALTER GOETERS, Deutsche med. Wchnschr. **80**:312 (March 4) 1955.

Forty-two children, 2 to 14 years of age, were treated with Uvilon, a piperazine preparation which is given by mouth. In 37 of the children, oxyuris disappeared without return over a period of 45 days.

AMBERG, Rochester, Minn.

RESULTS OF BCG VACCINATION IN THE NEWBORN. H. CZERMAK and A. ROSENKRANZ, Wien. klin. Wchnschr. **66**:489 (July 16) 1954.

The administration of BCG vaccine to the newborn infant is discussed. The procedure is without danger, as demonstrated by the results of 5000 vaccinations. The resulting positive tuberculin tests only regressed a few per cent when tested after one and two years.

AMBERG, Rochester, Minn.

Diseases of Nose, Throat, and Ear

THE CONDITIONED GALVANIC SKIN RESPONSE UNDER TWO MODES OF REINFORCEMENT. CLAY MERITSER and LEO DOERFLER, J. Speech & Hearing Disorders **19**:350-359 (Sept.) 1954.

The galvanic skin response in 56 subjects with normal hearing for 1000 cps was conditioned to appear upon auditory stimulus using electric shock as the unconditioned stimulus. One-half of the group received 40% reinforcement with the unconditioned stimulus; the other half received 100% reinforcement. Half of each subgroup was conditioned with a constant test of 30 db.; the other half was conditioned with a variable intensity of 30, 50, and 70 db. Reinforcement was then discontinued. One-half of each subgroup was extinguished at a constant intensity of 30 db.; the other half was extinguished at variable intensity. The 40% reinforced group showed greater resistance to extinction.

PALMER, Wichita, Kan.

A SPEECH RECEPTION THRESHOLD TEST FOR CHILDREN. BRUCE SIEGENTHALER, JACK PEARSON, and RAYMOND LEZAK, J. Speech & Hearing Disorders **19**:360-366 (Sept.) 1954.

A speech-hearing threshold test using picture identification techniques with carefully selected stimulus words and pictures for children as young as 3 or 4 years is described. The test meets the special needs of children, has a close relationship with spondee threshold for a group of adults, and high correlation with pure-tone loss.

PALMER, Wichita, Kan.

ASPIRATION LEVELS OF DEAF CHILDREN AS COMPARED WITH THOSE OF HEARING CHILDREN. LOUIS RUTLEDGE, J. Speech & Hearing Disorders **19**:375-380 (Sept.) 1954.

Fifty-five institutionalized deaf children and 52 institutionalized hearing children completed a series of 10 goal-setting problems on two motor tasks (a balance test and an aspiration board). Significant and consistent differences between the two groups were obtained only on the tasks in which the deaf are handicapped.

PALMER, Wichita, Kan.

DIAGNOSIS AND THERAPY OF CHRONIC MAXILLARY SINUSITIS OF CHILDREN. H. WISSLER, H. ISELIN, and A. RÄBER, Schweiz. med. Wchnschr. **84**:688 (June 19) 1954.

The study of the symptomatology of 75 cases of chronic maxillary sinusitis in children has been reported previously. The incidence is given as about 50% of all patients with recurring infections of the respiratory tract. In children with normal upper respiratory tracts it was found in about 1%. Chronic cough is the most frequent symptom. The association with chronic bronchitis and bronchiectasis is stressed. The best diagnostic procedure is x-ray of the sinus. About one-third of the patients responded with complete cure to regular washings combined with penicillin injections. When this treatment is ineffective, surgery is indicated.

AMBERG, Rochester, Minn.

PROGRESS IN THE TREATMENT OF CAUSTIC LESIONS OF THE ESOPHAGUS AND THEIR SEQUELAE. K. BURIAN, Wien. klin. Wchnschr. **67**:162 (March 4) 1955.

Immediate treatment with cortisone in caustic lesions of the esophagus proved eminently beneficial, shortening the time of recovery and preventing the formation of stenosis. So far only one child with a very severe lesion has been treated with corticotropin (ACTH), but stenosing could not be prevented.

AMBERG, Rochester, Minn.

Diseases of Lungs, Pleura, and Mediastinum

HONEYCOMB LUNG AND XANTHOMATOSIS. A. M. MCDONALD and ROBERT A. SHANKS, Arch. Dis. Childhood **29**:127 (April) 1954.

Seven cases of honeycomb lung are described in which the causative condition was found to be a generalized xanthomatosis. It is suggested that in childhood xanthomatosis is the likeliest cause of this clinical and radiographic picture.

KELLY, Milwaukee.

AGENESIS AND HYPOPLASIA OF THE LUNGS: REPORT OF THREE CASES. A. BRETON and O. DUBOIS, Pédiatrie **9**:803, 1954.

Bilateral pulmonary agenesis is described in a twin who also showed other extensive malformations. The other twin had no demonstrable malformations. Two other cases of partial agenesis, in an 11-year-old boy and a 3½-year-old girl, are presented. In both cases infection led to surgical removal of the malformed lung.

The literature is reviewed and the embryology and possible pathogenesis discussed.

GLASER, Baltimore.

INTERSTITIAL PULMONITIS IN INFANTS. D. V. BORL, Minerva pediat. **6**:837 (Nov. 15) 1954.

Five cases of interstitial pnuemonitis in infants are reported. In none of the cases were antibiotics of any therapeutic value. Four of the patients died, and autopsy findings are reported. Following a realization that a Protozoa might be the causative agent, quinacrine (Atabrine) and Plasmochin were given to the fifth child and proved to be efficacious therapy; penicillin was also given to this child for prophylaxis against a bacterial complication.

HIGGINS, Boston.

THE SPASTIC BRONCHITIS IN EARLY CHILDHOOD. W. PLENERT, Deutsche med. Wchnschr. **80**:255 (Feb. 18) 1955.

Spastic bronchitis is differentiated from bronchiolitis as a disease of infants, with preponderantly expiratory dyspnea and inspiratory retractions. Spasms of the medium and finer branches are claimed to be its main features. Medication with Eupaco solution containing Eupaverin and atropine is given by injection. Its action is spasmolytic. It also proved efficacious in bronchiolitis. The dosage was 0.3 ml. in infants below 3 months of age, 0.4 ml. below six months, while the older children received 0.5 ml. as single doses. (The concentration of Eupaverin and atropine in the solution is not given.)

AMBERG, Rochester, Minn.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

INTUSSUSCEPTION IN INFANTS AND CHILDREN. DONALD S. THATCHER, Ann. Surg. **140**:180-184. (Aug.) 1954.

One hundred seventy-four cases of intussusception on record at Milwaukee Children's Hospital are reviewed.

The cases were studied in two groups, the first from 1923 to 1947 and the second from 1947 to 1953. Mortality rates in these two groups show a definite improvement.

Comparison is made with statistics reported from other pediatric surgical centers.

BANTIN, Omaha.

CHYLOUS CYSTS OF THE MESENTERY IN CHILDREN. J. C. HANDELSMAN and MARK M. RAVITCH, Ann. Surg. **140**:185-193 (Aug.) 1954.

True chylous cysts of the mesentery are so uncommon as to be considered among the rarest of abdominal tumors. Pathologically, the lesions may represent true lymphangiomata of the mesentery—the so-called chylangiomata—or may be lymphatic cysts resulting from obstruction.

Four cases are presented. In each instance pain was a prominent feature of the illness.

In each instance, resection of the cyst, mesentery, and intestine with end-to-end anastomosis was successfully carried out.

BANTIN, Omaha.

RUPTURE OF THE EXTRAHEPATIC BILE DUCTS FROM NONPENETRATING TRAUMA. LOCKERT B. MASON, J. BUREN SIDBURG, and SIXTO GUIANG, Ann. Surg. **140**:234-241 (Aug.) 1954.

Rupture of the extrahepatic bile ducts from nonpenetrating trauma is an infrequently encountered condition.

A presumptive diagnosis is made from a history of upper abdominal trauma followed by a brief period of shock, and later, in 24 hours to 2 weeks, the onset of jaundice, localized or generalized peritoneal fluid, and acholic stools. Light-colored bile by abdominal paracentesis confirms the diagnosis.

It is likely that there has been an occasional recovery when no treatment was given. Procedures which have been used are (*a*) repeated aspiration of the peritoneal bile; (*b*) celiotomy with drainage to the site of leakage; (*c*) anastomosis of a portion of the ductal system to the stomach or small bowel; (*d*) cholecystoenterostomy; (*e*) cholecystostomy, and (*f*) attempts at direct repair of the ducts.

The authors report two cases and discuss the advantages and disadvantages of the various surgical procedures.

BANTIN, Omaha.

Nervous Diseases

DETERMINING THE SITE OF BRAIN TUMORS: THE USE OF RADIOACTIVE IODINE AND PHOSPHORUS. EDWIN W. AMYES, PAUL H. DEEB, PHILIP J. VOGEL, and RALPH M. ADAMS, California Med. **82**:167 (March) 1955.

By tests using radioactive iodine combined with diiodofluorescein, the site of tumors was correctly determined in 61% of 39 cases of tumors of the cerebral hemispheres. In 19 cases where the focal radioactivity was increased 24% or more over that of the surrounding area, there were no errors in localization. Fifteen patients with expanding intracranial lesions were tested at operation with radioactive phosphorus, and 14 lesions were correctly localized. This procedure in which the needle probe was used was found of great value in rapidly locating and outlining the area of involvement.

PRYOR, Redwood City, Calif.

ANTIDROOL MASK FOR CHILDREN WITH CEREBRAL PALSY. S. MALVERN DORINSON, J. A. M. A. **155**:439 (May 29) 1954.

Spastics who drool because they can't swallow properly must swallow or choke if their mouths are held shut. A mask over the mouth for 30 minutes has made these patients swallow as much as 120 times.

KIMBALL, Evanston, Ill.

A PARENT TRAINING PROGRAM FOR A CEREBRAL PALSY UNIT. HELEN J. LEVINSON, J. Speech & Hearing Disorders **19**:253-257 (June) 1954.

The author gives an outline of the parent-education project of P. S. 67, Brooklyn, carried on in five group sessions, each lasting one and one-half hours once each month. A considerable amount of practical help for parents was obtained during the program.

PALMER, Wichita, Kan.

MYSOLINE. WILLIAM H. TIMBERLAKE, JOHN A. ABBOTT, and ROBERT S. SCHWAB, New England J. Med. **252**:304 (Feb. 24) 1955.

Mysoline is an effective anticonvulsant in patients with psychomotor automatisms, grand mal, and focal motor and myclonic seizures, giving complete to excellent control in 54%.

Its principal side-effects are drowsiness and ataxia. Only one patient may have had a disturbance of blood formation due to Mysoline combined with mephobarbital (Mebaral). No kidney or liver damage was encountered.

By starting with half a tablet of Mysoline at bedtime and very gradually increasing the dose, tolerance can be built up in the body and side-effects can be minimized. Infrequently, a severe reaction may follow even a small initial dose. However, this may not recur later, and the patient may go on to tolerate doses effective in controlling his spells.

FROM THE AUTHORS' SUMMARY.

THE ATHETOID SYNDROME IN CEREBRAL PALSY: PART I: ETIOLOGY. STANLEY S. LAMM and LEO J. KOVEN, Pediatrics **14**:130 (Aug.) 1954.

Athetosis in infancy and childhood is primarily the result of anoxia associated with the birth of the infant. A secondary factor is icterus and Rh incompatibility, especially in the deaf athetoid. The family background and period of pregnancy appear to play no role in the etiology of athetosis. The order of pregnancy is highly significant, the risk of pathology being enhanced with the first delivery. The finding that anoxia plays the paramount role is consistent with proved pathological studies which have revealed changes in the brain associated with anoxia.

The incidence of athetosis may be lessened if the primary factors which lead to anoxia, Rh incompatibility and icterus are avoided or controlled. FROM THE AUTHORS' SUMMARY.

ASYMMETRICAL WIDENING OF THE CORONAL SUTURE SECONDARY TO AN INFECTED SUBDURAL HEMATOMA. ELMER G. ST. JOHN, Radiology **63**:246-247 (Aug.) 1954.

Infected subdural hematomas often cause bulging and thinning of the calverium overlying the lesion, but unilateral separation of the cranial sutures is rare. Such a case is reported. The lesion was located beneath the left portion of the coronal suture, causing it to separate.

ANSPACH, Riverside, Ill.

PURULENT MENINGITIS IN INFANCY AND CHILDHOOD. JOHN BEVERIDGE, M. J. Australia **1**:932-937 (June 19) 1954.

The author states that he makes no attempt to tell how meningitis should be treated, but explains the strategy and tactics which have been employed at the Royal Alexandra Hospital for Children.

Treatment of 110 patients suffering from purulent meningitis is presented. The survivors have been followed after their discharge from the hospital.

Cases of neonatal meningitis, pneumococcal meningitis, and influenzal meningitis are discussed. Some suggestions are offered as to how the regimens of treatment used may be modified.

McGUIGAN, Evanston, Ill.

DOES THE pH OF THE CEREBRO-SPINAL FLUID INTERFERE IN THE TREATMENT OF PURULENT ACUTE MENINGITIS OF CHILDREN: SIGNIFICANCE OF THE pH IN THOSE SOLUTIONS INJECTED BY INTRATHECAL ROUTE. C. PAGUE, Presse méd. Supp. 66, p. 1364, Oct. 9, 1954.

There may be some cases of purulent meningitis in children in which an oral or parenteral therapy very early applied proves unquestionably effective; yet there are other advanced cases for which an intrathecal treatment is necessary.

From his investigations into the literature and from his personal observations, the author has been led to consider the role of the pH of the cerebrospinal fluid regarding the side-effects subsequent to intraspinal introduction of medicamentous substances. Accidents are not likely to occur when the pH of these substances is about the same as that of the cerebrospinal fluid, the adequate dosage to be used being evaluated in relation to the tolerated pH and not to the body weight of the patient.

The author claims that the spinal cord and nervous parenchyma are not usually adapted to withstanding a sudden alteration of the cerebrospinal fluid pH following intrathecal, ventricular, suboccipital, or lumbar injection.

When this is to be performed into a clear cerebrospinal fluid with a rather normal pH, the solution to be injected must be of a similar pH (from 7.3 to 7.6 in the average of cases), so that any side-effect might be avoided.

It appears to the author that further researches should be carried out in order to determine the conduct to adopt when a subarachnoidal injection is indicated in the presence of these two clinical eventualities—purulent cerebrospinal fluid and rather normal cerebrospinal fluid.

FROM THE AUTHOR'S SUMMARY.

VIRAL AND SIMILAR MENINGOENCEPHALITIDES. R. MIRAPEIX TURC, Arch. pediat., Barcelona **4**:359-377 (Jan.-Feb.) 1954.

The clinical symptoms of nonbacterial meningoencephalitides are usually an abrupt acute meningeal type onset with no evidence of spinal fluid changes. Neither microscopically nor by culture can organisms be demonstrated. The course is usually short, benign, and without sequelae. This group of diseases does not show the epidemiological characteristics of most infections. There is a complicated relationship, especially in those where animal carriers are involved. The author shows the complicated relationship between the human and murine forms of choriomeningoencephalitis taken from the work of Duncan Thomas and Tobin.

Among the others discussed are meningeal involvements due to Coxsackie or pseudopoliomyelitis of Jungeblatt, lethargic encephalitis, and St. Louis equine encephalitis.

Some viruses are always neurotropic, and others are not. Among the viruses which may or may not cause meningoencephalitis are poliomyelitis, epidemic parotiditis, herpes simplex, herpes zoster, and measles.

The various forms of leptospiral meningoencephalitides are differentiated. Protozoan organisms include the Toxoplasma. Ricketoidal bodies may be responsible, as in Q fever, and lastly, such fungus pathogens as Torula histolytica may cause the meningoencephalitis.

Other causes may be termed sympathetic or concomitant, where the infection is elsewhere in the body but gives meningeal symptoms, or allergic responses may be responsible. Last of all, toxic agents may be responsible.

The purpose of the paper is to call for better cooperation between veterinarians and physicians and to protest against the use of the diagnosis of abacterial or serous meningoencephalitis.

ALLEN, Santa Fe, N. Mex.

PHOTOGENIC EPILEPSY. GERHARD SCHAPER, Monatsschr. Kinderh. **102**:508-514 (Dec.) 1954.

Two children with photogenic epilepsy are described in this report. In the history of both patients, intermittent light stimulation seemed to trigger off myoclonic seizures. This cause-and-effect relationship was confirmed during hospitalization and corroborated by electroencephalography.

HARTENSTEIN, Syracuse, N. Y.

ELECTROCARDIOGRAPHIC STUDIES DURING PNEUMOENCEPHALOGRAPHY. GERHARD SCHAPER, Monatsschr. Kinderh. **103**:14-17 (Jan.) 1955.

Electrocardiographic studies shortly before, during, and shortly after pneumoencephalography were performed in 50 children. Ages ranged from 9 days to 14 years. There were 27 boys and 23 girls. Only five patients had normal pneumoencephalograms, whereas ventricular changes, cysts of the septum pellucidum, microcephaly, and other pathological changes were demonstrable in all the other patients. Electrocardiographic tracings were obtained within a few hours before, during, and within two hours after pneumoencephalography.

The following electrocardiographic changes were noted during air injection:

Tachycardia	40 times	Q-T shortening	9 times
Bradycardia	26 times	S-T depression	23 times
P wave changes	13 times	Flattening or inversion of T waves	19 times
Interference dissociation	24 times	Diphasic T waves	5 times
Nodal rhythm	22 times	T wave elevation	11 times
Extrasystoles	18 times	U waves	7 times
A-V dissociation	1 time	Delayed conduction	4 times
Q-T prolongation	13 times		

In two patients no electrocardiographic changes were noted. All changes were reversible within two hours after pneumoencephalography.

There was no correlation between electrocardiographic changes and age, sex, degree of ventricular filling, and shape or size of the ventricular system.

It was postulated that cerebral extracardiac factors due to vagal stimulation were responsible for the electrocardiographic changes.

HARTENSTEIN, Syracuse, N. Y.

Psychology and Psychiatry

MANIA IN CHILDHOOD: REPORT OF A CASE. JAMES F. MCHARG, A. M. A. Arch. Neurol. & Psychiat. **72**:531-539 (Nov.) 1954.

A case of manic-depressive psychosis in an 11-year-old girl is discussed. Complete remission without special psychotherapy occurred after 16 weeks. There was a family history of manic-depressive psychosis.

MCGUIGAN, Evanston, Ill.

A PROGRAM OF TREATMENT FOR RETARDED CHILDREN. JAMES T. SHELDON, California Med. **82**:388 (May) 1955.

Mental retardation is a symptom of an underlying disease process. In California state hospitals for the retarded an accurate dynamic diagnosis is possible through utilizing the knowledge of neurology, psychiatry, pediatrics, psychology, social service, rehabilitation, education, the laboratory, and trained psychiatric technicians. A program of "custody" is archaic, and we are returning to the concept of training, treatment, and turnover. This kind of program is essential in order to avoid building new hospitals at the cost of millions of dollars every few years.

Parent organizations for retarded children are expanding in ever-increasing numbers. Special education programs in public schools, foster care homes, and sheltered workshops may make admission to hospitals unnecessary and aid return of patients to the community.

PRYOR, Redwood City, Calif.

ENURESIS: A CRITICAL REVIEW OF THE SYMPTOM. JOSEPH D. TEICHER, California Med. **82**:392 (May) 1955.

Enuresis is a symptom for which many kinds of treatments ranging the gamut of unscientific medical practices have been tried. To establish bladder control at the appropriate age is important because it means self-control, one of the foundations of a healthy personality. In most children with enuresis there has been no convincing demonstration of organic pathology of the urinary system. The cure of enuresis lies in the correction of psychological causal factors, such as sibling jealousy, suppressed hostile feelings, and sex difficulties. Routine urologic investigation of enuresis is unwarranted and unkind, unless there is a valid medical indication. Any therapeutic program for enuresis should center upon the child and not his bladder.

PRYOR, Redwood City, Calif.

PATHOGENESIS OF READING DISABILITY. MILDRED GIGNOUX DOWNES and RITA S. SCHUMAN, New England J. Med. **252**:217 (Feb. 10) 1955.

The authors attempt to elucidate what is known about why some children can read and some cannot. The variations in this disability are briefly described and its ancillary symptoms and signs enumerated. The following tentative conclusions as to causation are given: (1) the disabled reader lives in a poorly unified world; (2) he feels inadequate and inferior and is anxious; (3) he must enter school at rigidly prescribed ages whether he is prepared or not; (4) he may have developed "psychic deafness" in regard to his controlling adult world.

WHEELOCK, Washington, D. C.

INFANT FEEDING AND EMOTIONAL SECURITY. O. WILLIAM ANDERSON, Northwest Med. **54**:134 (Feb.) 1955.

This is a somewhat philosophical discussion of infant feeding and its effects on the infant, the infant's mother, and the doctors prescribing the schedules and foods. The article gives a historical background for the present varied concepts of infant feeding. It concludes with a plea for regularity and monotony in infant diets.

DOCTER, Seattle.

THE IMPORTANCE OF CHILD PSYCHIATRY. LUIS FOLCH CAMARASA and RAMON BASSOLS PARÉS, Acta pediát. españ. **12**:250-259 (March) 1954.

The authors discuss the part the pediatrician can play in assisting in a diagnosis as well as help he can give to parents and children in the field of behavior problems and other difficulties of personality development.

Dynamic psychology has unearthed many well-documented facts concerning early development of the child. Brilliant successes have been achieved by psychotherapeutic techniques. Basic concepts of child psychiatry include study of the child on both conscious and subconscious planes by such techniques as play therapy and drawing. The concept of transference between the child and the physician or therapist is an important one, as is work with parents to alter traumatic processes in the child's environment.

Therapy should not be limited to simple resolution of the child's conflicts but should assist him to reconstruct his personality. In this area the pediatrician may practice a certain amount of psychotherapy; he should remember that the whole child suffers whether the cause of his illness is organic or psychogenic.

ALLEN, Santa Fe, N. Mex.

THE MOTIVATION FOR FIRST CONSULTATION IN CHILD PSYCHIATRY. LUIS FOLCH CAMARASA and RAMON BASSOLS PARÉS, Acta pediát. españ. **12**:259-266 (March) 1954.

The authors present statistics regarding children treated at the Section on Child Psychiatry in the Dispensary of Santa Cruz and San Pablo, in Barcelona.

They discuss reasons given for the consultation and the importance of a positive attitude toward the referral. The most important factor in treatment is the family attitude. Much better results can be achieved if the family accepts treatment rather than having it come as a result of the demand of schools. Although there has been much improvement, cases are still referred rather late in many instances.

The majority of the cases are referred for behavior problems.

ALLEN, Santa Fe, N. Mex.

A TRIAL WITH THE TREATMENT OF MENTALLY RETARDED CHILDREN WITH OATMEAL. BERNDT LOTTNER, Deutsche med. Wchnschr. **79**:1837 (Dec. 3) 1954.

Thirty-three children requiring special schooling were given oatmeal flakes (not cooked) with some milk, fruit, and nuts for breakfast about three-quarters of an hour before the lessons, for about two and one-half months. Decrease of restlessness and fatigability, and increased capacity of concentration were noted. The same emotional improvements were seen as with isolated amino acids or mixture of amino acids.

AMBERG, Rochester, Minn.

EXPERIENCES WITH GLUTAMIC ACID TREATMENT OF MENTAL DEFICIENCY IN CHILDREN. Z. KUNCOVA, Pediat. listy **8**:14, 1953.

Glutamic acid was administered to 222 mentally defective children (15 personally observed ones). None of these children have improved so as to become normal members of the children's collective. A certain improvement in some of the children could be accounted for by the effect of the glutamic acid as well as by the increased educational effort of the environment.

FROM THE AUTHOR'S SUMMARY.

STUDY OF NERVOUS BEHAVIOR DISORDERS IN SCHOOL CHILDREN IN THE FOUR LOWEST SCHOOL CLASSES. E. GEDDA, Svenska läk. tidning. **50**:763 (April 2) 1953.

Out of 391 children who displayed behavior disorders at the start of the school years during the first four years of school, 19.2% had lost their nervous symptoms, 29.6% were improved, 21% were unchanged, and 9.2% were worse; 21% of the children had gone to other schools. Out of the 488 children who, when they started school at 7 years of age, were regarded as healthy and displayed no behavior disturbances, 25% had acquired such disturbances during the first four years; 18.6% of the children had gone to other schools.

WALLGREN, Stockholm.

Diseases of Genitourinary Tract

HERNIAS AND HYROCELES IN INFANTS AND CHILDREN. JOHN L. KEELEY, Illinois M. J. **105**:1-4 (Jan.) 1954.

According to Keeley, hernial sacs are found in a surprisingly high percentage of patients with hydroceles if a search is made for them. Hernias and hydroceles are more commonly found in male infants and children, and hernias are more often on the right side. A narrow communication between the processus vaginalis and the peritoneal cavity may persist and permit peritoneal fluid to pass through slowly, though it is not large enough to permit entrance of the small bowel. Although efforts to reduce the swelling promptly by external pressure are unsuccessful, the swelling usually disappears after a night's rest in the recumbent position.

Frequently one is forced to conclude that a hernia is present on the basis of the history alone. In addition to the mother's history, it is helpful, especially in unilateral cases, to find thickening of the structures of the cord at the external ring. If doubt exists that a hernia is present, further observation and repeated examinations are indicated.

In a young patient, an incarcerated hernia should be released, if possible, by elevation of the lower extremities, using gravity to reduce the contents of the sac and influence the circulation and edema favorably. Appropriate sedation may be given. As an elective procedure whenever the diagnosis of hernia is made, repair is indicated. The earlier the repair is done, the less chance there is of incarceration. The combination of hernia and hydrocele is not unusual.

BARBOUR, Peoria, Ill.

Diseases of Ductless Glands; Endocrinology

HISTOCHEMICAL DEMONSTRATION OF DISULFIDE GROUPS IN THE NEUROHYPOPHYSIS UNDER NORMAL AND EXPERIMENTAL CONDITIONS. RUSSELL J. BARRNETT, Endocrinology **55**:484-501 (Oct.) 1954.

The present studies demonstrate that the infundibular processes of the neurohypophyses of normal rats and other animals contain disulfide-positive colloid-like structures which appear to be the same as neurosecretory material. A hypothesis is presented suggesting that the migration of neurosecretory material from hypothalamic neurons to the neurohypophysis may be correlated with differences in the blood vessels within and outside of the blood-brain barrier.

JACOBSEN, Buffalo.

CORTISONE-INDUCED CONGENITAL CLEFT PALATE IN RABBITS. THEODORE FAINSTAT, Endocrinology **55**:502-508 (Oct.) 1954.

When pregnant mice were treated with large doses of cortisone, they frequently resorbed their litters. Subresorptive doses of cortisone were given, and a variety of congenital defects were present among the newborn. Cleft palate was the most frequently visible gross defect. Greatly reduced birth weights and a very high incidence of stillbirths were evident. The response to cortisone treatment, as measured by the incidence of cleft palate, was markedly influenced by the genetic make-up of the animals. Parallel experiments on rabbits yielded similar results. It is suggested that these phenomena are probably applicable to many other mammals, perhaps inclusive of humans.

JACOBSEN, Buffalo.

CORTISONE AND PHAGOCYTOSIS. JOHN H. HELLER, Endocrinology **56**:80-85 (Jan.) 1955.

Cortisone has been demonstrated to reduce the resistance of mammals to bacteria, viruses, fungi, and bacterial toxins. It has been suggested that the effect must be on the reticuloendothelial system (RES). This paper concerns itself with further investigation into the specific nature of the effect of cortisone on RES functions involved in infection.

By the use of negatively charged colloidal $CrP^{32}O_4$ it is possible to measure certain functions of the RES. Using this method of measurement, it appears that cortisone depresses the ability of the RE cells to phagocytize and regenerate.

JACOBSEN, Buffalo.

PREVENTION OF ADRENAL CORTICAL HYPERTROPHY IN DIABETIC RATS BY THE USE OF INSULIN. JAMES B. FIELD, Endocrinology **56**:499-506 (May) 1955.

The present study was undertaken to determine whether insulin would prevent the adrenal cortex hyperactivity of diabetic rats.

In an acute experiment lasting 72 hours, adrenal cortex hypertrophy was prevented in diabetic rats by regulating the diabetes with insulin. When the experiment was prolonged to three weeks, the results were inconclusive.

JACOBSEN, Buffalo.

THE ROLE OF THE PITUITARY AND THYROID GLANDS IN THE PHOSPHORUS METABOLISM OF THE ADRENAL GLAND DURING COLD STRESS. DORIS NICHOLLS and R. J. ROSSITER, Endocrinology **56**:547-559 (May) 1955.

Evidence is presented for the view that the early (three hours in the cold) response in the phosphorus metabolism of the adrenal gland of rats exposed to cold is caused by endogenous corticotropin (ACTH) liberated from the pituitary. The later response (several days in the cold) is, in part at least, dependent upon the activity of the thyroid gland.

JACOBSEN, Buffalo.

INDEPENDENCE OF ADRENAL HYPERPLASIA AND GONADAL MASCULINIZATION IN THE EXPERIMENTAL ADRENOGENITAL SYNDROME OF FROGS. CHIH-YE CHANG and EMIL WITSCHI, Endocrinology **56**:597-605 (May) 1955.

The similarity of the estrogen-induced adrenal and gonadal effects in larval frogs with the characteristic picture of the so-called adrenogenital syndrome of human pathology has been pointed out.

It is concluded that under the conditions of the present experiment the hyperplastic adrenal has no androgenic functions. Adrenal hyperplasia and sex reversal are independent responses to the estradiol administrations.

JACOBSEN, Buffalo.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

ACUTE SUPPURATIVE ARTHRITIS OF THE HIP IN PREMATURE INFANTS. DONALD W. ROSS, J. A. M. A. **156**:303 (Sept. 25) 1954.

Five cases of acute suppurative arthritis of the hip in the premature are reported in detail. In only one of the five was the diagnosis made promptly, and thus permanent damage was avoided. Whenever there are local signs of inflammation in the groin, buttock, or thigh, then a pyoarthrosis should be considered, which can be proved by the aspiration of pus. If treatment is delayed until there are roentgenographic changes, then the damage to the joint is usually extensive and crippling.

KIMBALL, Evanston, Ill.

SURGICAL TREATMENT OF FUNNEL CHEST DEFORMITIES IN CHILDREN. ROLAND D. PINKHAM, Northwest Med. **54**:477 (May) 1955.

The author discusses the theories as to etiology, prognosis, complications, and reasons for advising surgical correction for funnel-chest deformities in children.

He further discusses the operative procedures and results in a series of 26 cases as followed in one clinic. To date the operative results have been disappointing.

DOCTER, Seattle.

EPIPHYSEAL STAPLING FOR KNOCK KNEE. M. F. PILCHER, Great Ormond St. J., No. 7, pp. 37-42, June, 1954.

Fourteen cases of knock-knee were treated by epiphyseal stapling. The method has the advantage of being quick and reasonably exact and requiring only a short hospitalization, without plaster casts. Occasional staples may be expended and have to be replaced once or twice, and there is some slight risk of premature closure of the epiphysis. On the whole, however, the operation merits extensive trial.

MCGUIGAN, Evanston, Ill.

A Congenital Osteopathy Eventually Familial in Character and Especially Defined by Anteroposterior Incurvation and Thickening of Both Bones of the Lower Extremity. R. Weismann-Netter and L. Stuhl, Presse méd., Supp. 78, p. 1618, Nov. 24, 1954.

The authors point out that the deformity characterized by the thickening and anteroposterior incurvation of both bones of the lower extremity, as exemplified here by seven cases, is not due to rickets, contrary to general opinion. It is independent of rickets, although the shortness in stature, which is only confirmed by puberty, and the morphology of the pelvis might be suggestive of a rachitic origin. It is a congenital and familial deformity, for which neither heredosyphilis, nor dysendocrisiasis, nor other visceral disorders are responsible. This statement is confirmed by the case histories here reported.

The condition is neither painful nor even functionally much disturbing in both sexes, particularly when the form is bilateral and symmetrical. It is only relevant to genetics and justifies the term "congenital diaphyseal tibio-fibular toxo-pachyostosis" suggested by the authors.

From the Authors' Summary.

Lymphogranuloma Malignum in Tuberculosis. Paolo Prosperi and Angelo Ulivelli, Rev. clin. pediat. **54**:245 (Oct.) 1954.

The authors carried out a statistical study on various factors (sex, age, duration, localization, radiological and hematological findings, biopsy, itching, and association with other diseases) deduced through the observation of the case histories of 33 patients suffering from the Hodgkin's disease and attending the Florence University Children Hospital during 44 years.

From the various statistical data it stands out that the percentage of Hodgkin's disease cases associated with tuberculosis is 15.1%.

The authors conclude that the statistical study does not allow them to state a real reciprocal relationship between the two diseases, though the tuberculosis takes second place in the statistics of the diseases associated with malignant lymphogranuloma.

From the Authors' Summary.

The Differential Diagnosis of Periostitis in Early Childhood. Johannes Oehme, Monatsschr. Kinderh. **102**:514-522 (Dec.) 1954.

Based on actual cases, periostitis in children is classified as follows:

1. Congenital syphilis
2. Vitamin metabolism disturbances
   - (*a*) Vitamin deficiences
     - (1) Lack of vitamin C
     - (2) Lack of vitamin D
   - (*b*) Overdosage of vitamins
     - (1) Hypervitaminosis A
     - (2) Hypervitaminosis D
3. Osteomyelitis and sepsis
4. Diseases of bone
   - (*a*) Tuberculosis
   - (*b*) Osteopetrosis (marble bones)
   - (*c*) Sarcoma of bone
   - (*d*) Albright's disease
   - (*e*) Paget's disease
   - (*f*) Von Recklinghausen's disease
   - (*g*) Infantile cortical hyperostosis
   - (*h*) Eosinophilic granuloma
   - (*i*) Disease of calcium metabolism
5. Trauma—postnatal or at birth

6. Blood diseases—leukemia, osteomyelosclerosis
7. Skin diseases
   (*a*) Urticaria pigmentosa
   (*b*) Congenital ichthyosis
   (*c*) Pyoderma
8. Pseudoperiostitis
   (*a*) Errors in projection of x-ray
   (*b*) Disturbances in growth, such as in premature infants (reversible without specific treatment)

HARTENSTEIN, Syracuse, N. Y.

Cutaneous Diseases; Allergy

SEQUENCE OF HISTOLOGIC CHANGES IN SKIN OF DOGS IN RELATION TO DIETARY FAT. ARILD E. HANSEN, JOHN G. SINCLAIR, and HILDA F. WIESE, J. Nutrition **52**:541 (April 10) 1954.

Hansen, Sinclair, and Wiese have presented findings that suggest that dietary fat supplies a factor necessary for the maturation of epithelial, sebaceous, and sudoriparous cells which, when absent from the diet, results in distinct abnormality in the skin of dogs and puppies, demonstrable both microscopically and grossly. When fat is added to the diet, the process is readily reversible. They conclude that there seems to be little doubt that the chemical, physiological, and histological changes which are observed following prolonged use of a low-fat diet are due to the lack of unsaturated fatty acids, which are not synthesized by various animal species in sufficient amounts for storage to meet their needs for these fatty acids. These animals all received a high dietary intake of vitamin A, and the blood levels also were high and in the same range for both control and low-fat animals. It was suggested that linoleic acid supplies a necessary component for the structure of certain cells which permits them to complete their life cycle.

FREDEEN, Kansas City, Mo.

TREATMENT OF SCABIES AND OF PEDICULOSIS, WITH GAMMA-HEXACHLORCYCLOHEXAN (ATAN). H. SPÜHLER, Schweiz. med. Wchnschr. **84**:701 (June 19) 1954.

Very good results were obtained in cases of scabies with Atan in the form of a 1% ointment. Since Atan kills the ova, as demonstrated, only one treatment is necessary. In a number of cases of scabies, as well as pediculosis pubis or capitis, no recurrence was noted.

AMBERG, Rochester, Minn.

BIOTIN IN THE TREATMENT OF ERYTHRODERMIA DESQUAMATIVUM AND SEBORRHEIC DERMATITIS. S. PETROCINI and P. DEBERNARDI, Lattante **25**:360 (June) 1954.

Biotin, given intramuscularly or orally, was found efficacious in relieving the skin conditions in small infants with Leiner's disease or with seborrheic dermatitis. Biotin was found to be of no value in the treatment of infants with eczema.

HIGGINS, Boston.

Teeth and Dentistry

DENTAL CARIES IN THE COTTON RAT: XIV. FURTHER STUDIES OF CARIES PRODUCTION BY NATURAL DIETS WITH ESPECIAL REFERENCE TO THE ROLE OF MINERALS, FATS, AND THE STAGE OF REFINEMENT OF CEREALS. MARGUERITE A. CONSTANT, H. WILLIAM SIEVERT, PAUL H. PHILLIPS, and C. A. ELVEHJEM, J. Nutrition **53**:17 (May 10) 1954.

The purpose of this report, as stated by Constant and co-workers, was to present data on the effect of certain minerals, dietary fat, tooth maturity, and processed cereals on the production of dental caries in the teeth of cotton rats. Calcium carbonate, disodium phosphate, basic salt mixtures with and without calcium, and near neutral salt mixtures containing calcium retarded the development of caries in the erupted tooth. Low-mineral natural diets which produced extensive tooth decay when fed to weanlings were found to be relatively noncariogenic if fed to older animals. When substituted for the "natural" fat of a cereal-milk diet, oily fats, such as corn oil or butter, were found to give partial protection against tooth decay.

FREDEEN, Kansas City, Mo.

DENTAL CARIES IN THE COTTON RAT: XV. THE EFFECT OF TOOTH MATURITY AND MINERALS ON CARIES PRODUCTION BY SEMI-SYNTHETIC DIETS. MARGUERITE A. CONSTANT, H. WILLIAM SIEVERT, PAUL H. PHILLIPS, and C. A. ELVEHJEM, J. Nutrition **53**:29 (May 10) 1954.

Constant and co-workers presented the results of experiments which were conducted to study the effects of dietary calcium, tooth maturity, and acidic and basic salts on caries and to attempt to modify the cariogenicity of low-calcium diets. Increased tooth decay in the erupted tooth resulted when the calcium level was decreased. Withholding the cariogenic diets until the teeth were more mature decreased the caries susceptibility of the teeth. Acidic inorganic, basic, or acidic organic salt mixtures gave no protection against tooth decay. A high level of basic inorganic salts resulted in a marked decrease in tooth decay. Increasing the fat content to 15% did not protect against cariogenicity of a low-mineral synthetic diet. The addition of lysine or of tryptophan was without effect upon caries production obtained by feeding a low-calcium diet. The data on caries show that a reduction of the sucrose content of the basal from 60% to 20% did not result in a decrease in caries. On the contrary, there was a tendency toward increased caries development. The type of protein tended to modify the cariogenicity of a low-calcium diet. Albumin tended to produce less tooth decay, especially with regard to the extent of the lesions. A definite reduction occurred when fibrin was used. A combination of gelatin and casein had no effect.

FREDEEN, Kansas City, Mo.

EXPERIMENTAL RAT CARIES: EFFECT OF A NATURAL SALT MIXTURE ON THE CARIES-CONDUCTIVENESS OF AN OTHERWISE PURIFIED DIET. REIDAR F. SOGNNAES and JAMES H. SHAW, J. Nutrition **53**:195 (June 10) 1954.

Sognnaes and Shaw, from their observations in rats, have shown that the ingestion of the ash from a natural stock diet as the sole source of minerals during tooth development results in highly caries-resistant teeth. This source of minerals had its greatest significance in the offspring when its ingestion had been maintained by their mothers during pregnancy and lactation as well as by the offspring throughout the postdevelopmental caries-evaluation period. It is suggested that the observed caries protection may have resulted from the presence of certain trace elements in the ash mixture of the natural stock diet.

FREDEEN, Kansas City, Mo.

EXPERIMENTAL RAT CARIES: EFFECT OF FLUORINE ON THE CARIES-CONDUCTIVENESS OF A PURIFIED RATION. JAMES H. SHAW and REIDAR F. SOGNNAES, J. Nutrition **53**:207 (June 10) 1954.

Shaw and Sognnaes concluded that while flurides unquestionably modify the caries picture under certain conditions, their data suggest that there are other minerals or ratios of minerals which are major factors in determining the difference between sound and carious teeth.

FREDEEN, Kansas City, Mo.

TEETHING PATTERNS IN INFANCY. THEODORE JAMES, South African M. J. **28**:890-892 (Oct. 16) 1954.

The author is convinced that teething is frequently responsible for other symptoms, among which he lists cough, skin rash, diarrhea, vomiting, otitis media, recurrent bronchial catarrh, and convulsions. His observations are not detailed, and he cites no proof, but only a rather poorly elaborated hypothesis that the irritation of the tissues overlying the erupting tooth results in reflex irritation of other tissues of the same embryonic origin.

MCGUIGAN, Evanston, Ill.

Miscellaneous

CONSEQUENCES OF THE WIDESPREAD USE OF ANTIBIOTICS. LOWELL A. RANTZ, California Med. **81**:1 (July) 1954.

Great quantities of antibiotics are used each year. A direct result has been the appearance of large numbers of infections caused by organisms that are resistant to the action of one or more of these drugs. A new syndrome, that of superinfection by bacteria resistant to an antibiotic being administered, has become common. Its recognition is of great importance.

The control of resistant infections requires the development of new antimicrobial agents and new knowledge about the use of older ones in combination.

The medical profession must be circumspect in its use of these important drugs, or the time may come when the control of many serious infections may become impossible.

PRYOR, Redwood City, Calif.

INFECTIONS DURING CHEMOTHERAPY. LOUIS WEINSTEIN, MARTIN GOLDFIELD, and TE-WEN CHANG, New England J. Med. **251**:247 (Aug. 12) 1954.

Superinfection is a common complication of the use of antibiotics; it occurred in 2.19% of 3095 patients who were given a chemotherapeutic agent.

The organs involved in the secondary infection are most frequently the same as those affected in the primary disease.

The organisms responsible for the superinfection are often difficult to treat with the presently available antibacterial drugs.

The following factors predispose to the development of superinfection: age of 3 years or less; primary disease of the lower respiratory tract; infection of the middle ear; the use of a drug or combination of drugs that tends to have a "broad" antibacterial effect, and primary infection of the ear and secondary pneumonia.

Superinfection occurs most frequently on the fourth or fifth day after initiation of chemotherapy.

The appearance of superinfection during the administration of an antibiotic may convert a benign, self-limited disease into a serious, prolonged, or even fatal one.

It is essential to carry out frequent bacteriologic studies, whenever possible, to determine changes in bacterial flora that may subsequently be responsible for a secondary infection. The administration of an antibiotic active against the predominant organism before its involvement in infection may prevent the appearance of a complicating disease.

The data obtained in this study emphasize the danger of antibiotic therapy in diseases that are not treatable, since superinfection, which may be a very small risk in the untreated infection, may become a serious threat.

Chemoprophylaxis will not prevent secondary infection in many cases. Whether or not it actually reduces the incidence of superinfection in some diseases has not been accurately determined. This problem merits serious study.

FROM THE AUTHOR'S SUMMARY.

CHOLERETIC ACTION OF CORTISONE. PAUL R. PATTERSON, JOSEPH F. DINGMAN, HARRY SCHWACHMAN, and GEORGE W. THORN, N. England J. Med. **251**:502 (Sept. 23) 1954.

The authors present a pilot study in which the possible hydrocholeretic and choleretic actions of cortisone are demonstrated. A pancreozymic-like action of cortisone on the pancreas is also postulated. These observations may ultimately be of practical value to the pediatrician concerned with liver disease, biliary obstruction, and pancreatic insufficiency in infancy and childhood.

WHEELOCK, Denver.

PRESENT STATUS OF CHEMOTHERAPY IN CANCER. CORNELIUS P. RHOADS, New York J. Med. **54**:2557 (Sept. 15) 1954.

In this excellent study and report, Rhoads has brought to date the known facts concerning treatment of cancer by destructive agents produced within the body or introduced from without. He clearly states that many investigators have been working against wind and tide, without purposeful ends. Old procedures which have been found to be of doubtful value are still being reworked. Second, many have been awaiting some new concept in biology; therefore, much time and effort and money have been used to extend our knowledge of the natural sciences.

Chemotherapy for cancer in man, as limited, difficult, and noncurative as it is, offers a ray of hope. We can now produce cancer in lower animals by transplantation and can cure them. Not enough attention has been given to the cancer cell itself as a cancer-producing agent. Now we can inhibit the active growth of cancer in man temporarily, and destroy it completely in experimental animals.

A second advance in the chemotherapy of cancer came about during World War II in the use of nitrogen mustards, which are toxic to cancer cells. However, there are some disadvantageous by-products on normal cells in the mouth, intestinal mucosa, and hematopoietic structures.

Another observation: Cell division and propagation cannot go on save in the presence of folic acid. Therefore, if we could prevent folic acid from entering cancer cells, might we not starve these anarchists? Again, modified "adenines" are capable of blocking certain cells from reproducing.

An experimental result is well worth quoting: "In our laboratories, in experiments by Drs. Stock, Suguiara, Philips, Clarke, and their associates in more than 2,000 experimental animals bearing six different types of transplantable cancer, over 70 per cent of the neoplasms have been completely destroyed with cure of the hosts." Failure of the implanted tumor to grow in the treated animals when transplanted back ino the bodies of unreated animals shows that somehow inhibition was highly effective. Applying all this to man may not bring the expected and hoped for results, but it is highly encouraging to know that in nonhuman animals cancer can be cured!

Some satisfactory experiments with an agent known as Purinethiol in transient control of leukemia are of great interest. A symposium from 25 clinics showed remarkable uniformity of results. It was used in addition to cortisone and chemicals having antifolic activity, with a survival of children for over one year, an increase of from 29%-52%, enabling these children to lead fairly normal lives during the remission periods. Recurrence, however, is likely.

In summary, transplantable cancer can be completely destroyed in experimental animals. On occasion, certain cancers can be restrained in humans. Rhoads advances the hope that chemicals yet to be put together may eventually restrain or destroy cancer in humans.

I. W. Voorhees, New York [condensed from A. M. A. Arch. Otolaryng.].

The Use of a New Apparatus for Continuous Nebulization Therapy. Allan Bloxsom, South. M. J. **47**:819 (Sept.) 1954.

A modification of a DeVilbiss No. 40 Nebulizer is described with a 500 cc. reservoir and also a smaller reservoir. It has been used in conjunction with both the Gordon Armstrong incubator and a conventional oxygen tent. Penicillin, hyaluronidase, and Alevaire (alkylaryl polyether alcohol detergent) have been employed in the nebulized solution singly or in combinations. Diagrams of the apparatus are presented as well as a few illustrative case reports.

Logan, Rochester, Minn.

Blood Protein and Amino Acids in the Course of Treatment with Methylandrostenediol. P. Careddu, E. Depperu, and C. Vullo, Ann. ital. pediat. **7**:214 (Aug.) 1954.

The patterns of the proteins in blood and the amino acid output in the urine have been studied by paper chromatography in normal and malnourished children who have been treated with methylandrostenediol (M. A. D.). The results show a good anabolic activity of this steroid on the proteins.

From the Author's Summary.

Five Cases of Kerosene Poisoning. R. Purpura, Clin. pediat. **36**:367 (May) 1954.

Reports are given of poisoning from drinking kerosene by five children, aged 13 months to 4 years. The severity of the symptoms was proportional to the amount taken. The prevalent symptoms were cough, cyanosis, fever, agitation, and rapid pulse; there were rales at the lung bases and x-ray findings of bronchopneumonia. None of the children showed urinary abnormalities. Treatment was by stomach lavage, intravenous injections of dextrose solution, and antibiotics. Clinical recovery was obtained within five days; the x-ray findings in the lungs had cleared up in two weeks. The antibiotic therapy was of value only prophylactically.

Higgins, Boston.

Blood Levels After the Administration of Penicillin Orally. R. Minazza, Minerva pediat. **6**:534 (July 31) 1954.

Fifteen children, 3 to 7 years of age, were each given by mouth 300,000 units of penicillin (12,000 to 25,000 units/kg.). Assays of the blood for penicillin content were made one and one-half, three, and six hours after the ingestion. In each case, the titer showed amounts in excess of the minimum therapeutic level. Ten other children with bronchopneumonia, bronchitis, or tonsillitis responded very satisfactorily to oral penicillin therapy.

Higgins, Boston.

News and Comment

GENERAL NEWS

Specialists Certified by The American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., in New York, on June 10, 11, and 12, 1955.

Adler, Donald K., Woodmere, L. I., N. Y.
Alderfer, Harold Harr, West Chester, Pa.
Allen, Marvin Salisbury, Jamaica, N. Y.
Arey, Harriet Mitchell, Narberth, Pa.
Arnold, Harriet Jane, Bridgeton, N. J.
Axler, Morton Mitchell, Fort Eustis, Va.
Bedo, Andrew V., Mt. Pleasant, Mich.
Bergman, Cyril Albert, Fitchburg, Mass.
Bierly, Mahlon Z., Jr., Havertown, Pa.
Boyer, Paul Henry, New York
Brooks, Benjy Frances, Philadelphia.
Butson, Harry Eugene, Philadelphia.
Chamberlin, Harrie Rogers, Chapel Hill, N. C.
Cornely, Donald A., Drexel Hill, Pa.
Crane, Charles Herbert, Livingston, N. J.
Critz, George Theodore, Arlington, Mass.
Cullina, Helen K. O'Brien, West Hartford, Conn.
Davidson, Murray, Bayside, N. Y.
Davis, Kelley King, Wellesley Hills, Mass.
Dawson, George A., Methuen, Mass.
DeLaites, Loretta Mary, Chester, Pa.
DiGeorge, Angelo Mario, Philadelphia.
Dooley, Richard Robinson, Concord, Mass.
Eisner, Victor, Baltimore.
Essember, Lawrence, Danvers, Mass.
Farrell, Earl James, Jr., Fort Thomas, Ky.
Feldman, Arnold, Maplewood, N. J.
Frick, Adelaide, Short Hills, N. J.
Giannattasio, Rudolph Camillo, Brooklyn.
Grant, Donald Kerr, Cincinnati.
Griffin, John Wilder, Corsicana, Texas.
Guthrie, James R., Ossining, N. Y.
Hall, Glenn Claire, Jr., Radford, Va.
Hansen, Howard Edward, Los Angeles.
Harrington, Edwin D., Moorestown, N. J.
Homan, William Edmonds, White Plains, N. Y.
Horan, Jeanne Marcoux, New Orleans.
Hume, W. G. Mackenzie, Huntington, N. Y.
Hurwitz, Sidney, West Haven, Conn.
Kastner, Lee N., Portsmouth, Va.
Kearney, Paul A., Short Hills, N. J.
Krak, Michael, Dravosburg, Pa.
Kushino, Kenji, Chicago.
Lim, Wan Ngo, New York.
Lipschutz, Arthur, Philadelphia.
Lyons, David Robert, East Orange, N. J.
MacCollam, Allan, Albany, N. Y.
Mathieu, Peter L., Jr., Providence, R. I.
Mayer, Florence Emily, Chestnut Hill, Mass.
Moser, August W., Tenafly, N. J.
Newman, Leroy, Philadelphia.
Niermann, William Albert, Baltimore.
Nudelman, Jesse W., Floral Park, L. I., N. Y.
Peters, Earl Raymond, Annapolis, Md.
Raciti, Katina Aurelia, New Rochelle, N. Y.
Reichelderfer, Thomas E., Baltimore.
Richards, Roderick Clark, Scarsdale, N. Y.
Richlan, Alfred Ralph, Newark, N. J.
Riege, David Halsted, Hartford, Conn.
Rivers, Jane Andrews, Columbus, Ga.
Rivers, Walker Proileau, Jr., Columbus, Ga.
Robie, William Adlai, Annapolis, Md.
Sanders, David Sheldon, New York.
Schell, Norman B., Floral Park, N. Y.
Schnall, David J., Philadelphia.
Schulman, Jerome L., Baltimore.
Serra, Catherine Gilda, New Rochelle, N. Y.
Shipper, Harvey, Los Angeles.
Sims, Neil H., Annapolis, Md.
Sklar, Samuel, Highland Park, N. J.
Slater, Beatrice S., Riverdale, N. Y.
Slater, Robert J., Toronto, Canada.
Smith, William Clifford, Champaign, Ill.
Snyder, Eleanor N., Mill Valley, Calif.
Sonabend, David H., Long Beach, N. Y.
Stein, Howard Simon, Great Neck, N. Y.
Stern, Arthur Alexander, Pearl River, N. Y.
Swift, Sherrod Clinton, Whittier, Calif.
Vakiener, Jane Martha, Oradell, N. J.
Walker, Thomas English, Charlotte, N. C.
Wellemeyer, Jane, New York.
Winters, Harold V., Queens, N. Y.
Wolfish, Martin Gimpel, Toronto, Canada.
Yu, Wei-liang, New York.
Zaleznak, Bernard D., Brooklyn.

Books

Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. By Criteria Committee of New York Heart Association, Inc. Edition 5. Price, $4.95. Pp. 359, with 5 illustrations. New York Heart Association, Inc., 270 Park Ave., New York 17, distributed by American Heart Association, 1775 Broadway, New York 19, 1953.

This latest edition of the criteria has introduced new material and changed some of the former writing in accordance with knowledge gained during the past 10 years. The chapter on congenital anomalies has been rewritten. A new section on the subject of peripheral vascular diseases has been added. The chapters on roentgenology, electrocardiography, and pathological diagnosis of diseases of the heart have been extensively revised.

It is gratifying to note that the terms possible heart disease and potential heart disease have been dropped. The use of the word "innocent" to designate the murmurs thought not to be due to heart disease seems more appropriate than the terms previously used.

This authoritative little book continues to be an excellent guide to the general physician and to the worker in the cardiac clinic.

Year Book of Pediatrics: 1943-1954 Year Book Series. Edited by Sydney S. Gellis, M.D. Price, $6. Pp. 435, with 114 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1953.

This is the second of the "Year Book" series edited by Dr. Gellis. He continues his practice of submitting articles to consulting authorities so that their comments are included. This adds to the interest of the book and also minimizes the editor's possible bias. Under Dr. Gellis, the book has become even more interesting and valuable than before. It is heartily recommended as required reading for all pediatricians.

Chirurgie du nouveau-né et du nourrisson. By Bernard Duhamel. Price, 1920 francs. Pp. 308, with 158 illustrations. Masson & Cie, 120 boulevard Saint Germain, Paris 6e, 1953.

Based upon personal experiences and observations, the author has added an interesting volume to the subject of pediatrics by his description of the pathology and treatment of surgical diseases of the newborn and the infant. He emphasizes that the surgery of these little people is a true specialty and recommends in the handling of these cases a need for collaboration between pediatrician, otolaryngologist, and surgeon. Adequate examination, both physical and roentgenological, careful preoperative and postoperative attention, and well-administered anesthesia are stressed.

The body of the text is concerned with the surgical problems of the newborn and the infant. In the sections dealing with the pathology, many conditions are discussed which are frequently encountered on the surgical services of any large children's hospital. In the chapters limited to the newborn, many subjects are included, particularly those resulting from congenital malformations of the intestinal tract, such as tracheoesophageal fistula, stenosis, atresia, malrotation, duplications, and anomalous situations in the rectum and anus.

Mention is made of such congenital defects as omphalocele and certain tumors, such as angiomas and sacrococcygeal lesions. In the chapter on congenital malformations of the biliary tract, no reference is made to the Longmire procedure or the Roux-Y anastomosis in the surgical treatment of atresia or congenital absence of the choledochus. Meconium ileus and peritonitis are briefly considered. A chapter is devoted to a description of congenital diaphragmatic hernia in the newborn.

In the section limited to the pathology of the infant, congenital as well as acquired surgical diseases are discussed. Among the congenital group, discussion is confined to the surgical treatment of congenital hypertrophic pyloric stenosis, esophageal hiatus and inguinal hernias, management of congenital megacolon, and repair of cleft palate and harelip. Although medical therapy and splanchnicotomy are suggested, no mention is made of the use of surgical techniques, such as the Swenson procedure, in the correction of megacolon. Considerable emphasis is placed

on the etiology, clinical picture, diagnosis, and treatment of acute appendicitis and acute intussusception. One chapter is devoted to the discussion of the management of foreign bodies, accidental perforation, and stricture of the esophagus.

In general, this reviewer has the impression that the book comprises a review of the author's personal experiences in the care of surgical conditions found in the newborn and infant. Although the reader finds the various descriptions of interest, the material as a whole is not as all-inclusive as the masterpiece on surgical diseases of infants and children compiled by Dr. Robert Gross, of Boston. The author fails to mention special surgical techniques used in this country in the treatment of certain conditions. The surgery of bones and joints and the surgery of congenital malformations of the heart and great vessels are not a part of this book.

Triumph of Love. By Leona S. Bruckner. Price, $3. Pp. 213. Simon & Schuster, Inc., 630 Fifth Ave., New York 20, 1954.

Every physician is sometimes faced with the unpleasant duty of telling parents that their newborn child has some type of a handicap. When the child is a hopeles idiot or when he cannot survive because of a severe physical defect, the doctor encounters much less difficulty in this onerous task than when the child has a nonfatal physical deformity and normal mentality. A realistic interpretation to the parents of the nature of the problem before them is usually difficult to all concerned, since it must be done at a time when the parents are in a state of emotional turbulence. At times like this, it is often useful to have available a book which delineates the experiences, the spiritual anguish, and the mental processes of the parents of the disabled child, and the painful road to final acceptance.

Such a book is the present one, written by the mother of a child who was born a congenital bilateral arm amputee. The book is simply written and presents both the maternal and the paternal views. The problem that these parents faced was increased by the fact that they were told originally by a doctor that the child would be a hopeless idiot, that it would not survive, and they should not even bother to take it home from the hospital. The book should be valuable reading to parents who are faced with a similar problem. This volume differs from many of the others written by parents of handicapped children in that it does not have the undercurrent of parental martyrdom. Instead, it rather factually and charmingly depicts their problems. This book can be read with profit by doctors also, since it reflects the view of the layman to medical treatment which is sympathetic and understanding. It might help to remind them that curt and cold treatment of parents can never accomplish what a compassionate medical approach can do.

Alimentación del lactante: Técnica y educación alimentarias, profilaxis de los estados carenciales. By Arturo M. de San Martin. Price, 20 pesos. Pp. 76, with 8 illustrations. Editorial Artecnica, Buenos Aires, 1952.

The first part of this little book is devoted to the rather conventional details of infant feeding and includes such subjects as prenatal care and nutrition of the mother, with some mention of the anomalies which may develop in the first trimester of pregnancy from deficits in diet. He quotes Giroud and Minkowski regarding the deficit of riboflavin in such malformations as cleft palate, shortening of the extremities, and syndactylism. The lack of folic acid may result in ocular and facial malformations, and the teratogenic action of inadequate pantothenic acid may provoke anophthalmias and cerebellar lesions.

Some discussion is given to the treatment and prevention of hemorrhage of the newborn. Breast feeding and means of making this more comfortable and pleasant are discussed. The position as well as the feeling of well-being in both mother and baby is important. Illustrations of the "decubital-lateroventral position" show the baby and mother in a position comfortable to both. The mouth of the baby can search for the nipple, and he will not have an overwhelming thrust at his mouth.

Dr. San Martin believes also that the colostrum is of value in maintaining the integrity of the intestinal mucosa and preventing diarrhea of the newborn. The vitamin A content is exhausted at birth, and the colostrum can replenish this. Diarymen have long known that the newborn calf will develop diarrhea in the third week of life if it does not get colostrum.

The obscure cause of diarrhea of the newborn makes further study into this possibility important for research.

The details of artificial feeding and the pros and cons of self-demand feeding are fully discussed, with much detail of the history of infant feeding. The author believes in using more fats than are commonly used in the United States and gives some attention to the specific solid and semisolid foods commonly used in Argentina. Attention is also given to abnormalities in sleep and to vomiting and diarrhea, and, although he gives much attention to the psychological aspects, he also advises the use of drugs which may help.

By far his best contribution is his description of the oculomotor labial reflex. Every mother should be given a demonstration of this; there are several very pleasing photographs, as well as the painting by Albert Anker on the back of the book illustrating the ease with which a mother may use nature as a help in feeding her child. Using the well-known ability of a baby to fix on one object immediately in front of him, Dr. San Martin says the mother can hold the baby comfortably on her left side with her left arm supporting the child; the food is close to her right hand and by using the spoon poised right in front and somewhat higher than the baby's mouth, allow the baby to focus on each spoonful; the oculomotor labial reflex is easily demonstrated. As the mother gradually lowers the spoon toward the baby's mouth, the baby opens his mouth spontaneously. He even lowers his head a trifle to get at it, which Dr. San Martin calls a movement of reverence for food and an understanding mother. All toys, noises, and distracting things should be out of the way, and the mother, baby, and food should be the perfect triangle, or circle, if one prefers. This he says can be illustrated before students or mother, using a pencil or a tongue depressor.

To poke food at a baby whose mouth is shut only frustrates everybody because it is not based on sound developmental principles.

This little book should be a help to students, general practitioners, and pediatricians or nurses teaching pediatrics. Although much of it is of general interest to the parents, the first part is too technical for lay use. On the other hand, it is not detailed enough for a text, but could be a supplement useful to those interested in the feeding of children.

Directory of Pediatric Societies *

INTERNATIONAL

Eighth International Congress of Paediatrics

President: P. Plum Professor, M.D., Domus Medica, Kristianiagade, Copenhagen.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 16 rue du Mont Blanc, Geneva, Switzerland.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. Bernard Laski, Toronto.
Secretary: Dr. Crawford Anglin, Toronto.
Place: Academy of Medicine.

Asociación de Pediatrias Españoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marín and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Australian Paediatric Association

President: Dr. P. A. Earnshaw, Ballow Chambers, Wickham Terrace, Brisbane. B17.
Honorary Secretary-Treasurer: Dr. D. C. Jackson, 217 Wickham Terrace, Brisbane. B17.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Prof. Stanley Graham.
Honorary Secretary: Dr. Reginald Lightwood, Paediatric Unit, St. Mary's Hospital Medical School, London, W. C. 2.
Honorary Secretary: Dr. Philip Evans, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere. Time: Between Easter and Whitsunday.

Canadian Paediatric Society

President: Dr. G. R. Gayman, 710 Seymour St., Vancouver 2, B. C.
Secretary-Treasurer: Dr. J. C. Rathbun, 526 Waterloo St., London, Ont.

Clinical Pediatric Society of Israel

President: Dr. Stanley Levin, Government Hospital, Tiberias.
Vice-Presidents: Dr. Shimon Winter and Dr. George Mundel.
Place: Children's Departments of various hospitals. Time: Last Thursday of the month.

Danish Pediatric Society

President: Dr. A. Rothe-Meyer, Children's Hospital, Fûglebakken, Copenhagen F.
Secretary: Dr. E. Winge Flensborg, Children's Hospital, Martinsvej, Copenhagen V.
Place: Different hospitals. Time: First Wednesday of every month.

Departamento de Pediatria da Associação Paulista de Medicina

President: Dr. J. Leme da Fonseca.
Secretary: Dr. Joaquim da Costa Marques.

Departamento de Puericultura e Pediatria da Associação Medica do Parana

President: Dr. Haroldo Beltrao.
Secretary: Dr. Mucio de Ãbreu Neto.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. Dr. med. W. Keller, Freiburg/Brsg., Universitätskinderklinik.
Secretary: Prof. Dr. med. J. Jochims, Lübeck, Städtische Kinderklinik.
Place: Freiburg/Brsg. Time: September, 1955.

Hellenic Society of Pediatrics

President: Dr. A. Androutselli.
Honorary Secretary: Dr. A. Inglessi, 4 Milioni St., Athens.
Place: Lecture Theater, University of Athens. Time: Last Tuesday of each month, 7 p. m.

Israel Pediatric Society

Chairman: Prof. Sh. Rosenbaum, 26 Bialik St., Tel Aviv.
Secretary: Dr. R. Kochmann, 131 Ben Jehuda Rd., Tel Aviv.
Place: Tel Aviv.

Melbourne Paediatric Society

President: Dr. H. McLorinan.
Honorary Secretary: Dr. John H. Colebatch, 12 Collins St., Melbourne.
Place: Royal Children's Hospital, Melbourne. Time: Once monthly, February to December.

Nederlandse Vereeniging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. Henrik Hagelstein, Children's Department, Rikshospitalet, Oslo.
Secretary: Dr. Kare Havard Torp, Children's Department, Ullevål Hospital, Oslo.
Time: Friday, six times a year.

Pediatric Society of New Zealand

President: Dr. Edward J. Cronin, Power Board Bldg., Queen St., Auckland.
Secretary: Dr. J. D. Matthews, 104 Symonds St., Auckland.

Philippine Pediatric Society

President: Dr. Renato Ma. Guerrero.
Secretary: Dr. Felix A. Estrada.
Place: Santo Tomas University Hospital and other pediatric centers. Time: Every two months.

Royal Society of Medicine, Section of Paediatrics

President: G. H. Macnab, F.R.C.S.
Honorary Secretaries: Ursula James, M.R.C.P., and Leslie Scott, M.D.
Sectional Editor: D. MacCarthy, M.D.
Place: 1 Wimpole St., London W.1 (Correspondence for these honorary officers should be sent to this address). Time: Fourth Friday of each month, 4:15 p.m.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. W. Tobler, Brunnadernrain 11, Bern.
Vice-President: Prof. M. Jaccottet, Av. de Rumine, Lausanne.
Secretary: Dr. J. Haas, Westl. Alpenstrasse 3, Burgdorf.

Sociedad Argentina de Pediatrie

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chihuahuense de Pediatría

President: Dr. Alfonso Ruiz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

Sociedad Chilena de Pediatria

President: Prof. Dr. Raúl Gantes A.
Secretary-General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

Sociedad Colombiana de Pediatria

President: Dr. Alfonso Vargas Rubiano.
Vice-President: Dr. Darío Gutiérrez Laserna.
Secretary: Dr. Omar García Bustamante.
Treasurer: Dr. Alfonso Gutiérrez Reyes.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos y Gonzales.
Secretary: Dr. Carlos Hernandez Miyares, Apartado 2430, Habana.
Place: Catedra de Clinica Infantil Hospital Nuestra Senora de las Mercedes and Hospital Municipal de Infancia, Habana. Time: 9 p.m., last Wednesday of every month.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínico Regional, Concepción.
Place: Hospitnl Clínico Regional Concepción. Time: 7:30 p.m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatria del Litoral

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

Sociedad de Pediatria y Puericultura del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Hernando Barrios-Angulo.

Sociedade de Pediatria da Bahia

President: Dr. Elysio Pereira de Atbayde.
Secretary: Dr. Eliezer Audiface.

Sociedade de Pediatria de Pernambuco

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

Sociedade de Puericultura e Pediatria do Maranbão

President: Dr. Odorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

Sociedade Mineira de Pediatria

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

Sociedade Portugesa de Pediatria

President: Prof. Dr. Lucio de Almeida.
Vice-President: Dr. Cordeiro Ferreira.
Secretary-General: Prof. Dr. Carlos Salazar de Sousa.
Treasurer: Dr. Mario Cordeiro.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

Sociedad Uruguaya de Pediatria

President: Dr. Euclides Peluffo.
Secretary: Dr. Ruben Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. H. Arroyo Parejo.
Vice-President: Dr. Manuel M. Lander.
Secretary: Dr. Guillermo Tovar E., P. O. Box 3122, Caracas.
Treasurer: Dr. Carlos Lares Compos.
Place: Hospital Municipal de Niños "J. M. de los Ríos," Caracas. Time: Once a month.

Sociedad Yucateca de Pediatria

President: Dr. Humberto Perez Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

La Société de Pédiatrie de Montréal

President: Dr. Henri Charbonneau, 3095 Cherbrooke, Montréal.
Secretary: Dr. Edmond Baril, 301 Carré St-Louis, Apt. 1, Montréal.
Time: Second Thursday of each month.

Société de Pédiatrie de Paris

President: Prof. Jean Cathala, 45 rue Scheffer, Paris XVI.
Secretary: Prof. Maurice Lamy, 94 rue de Varenne, Paris VII.
Place: Hôpital des Enfants Malades, 149 rue de Sèvres, Paris XV. Time: 4 p.m., third Tuesday of each month.

Société de Pédiatrie de Québec

President: Dr. Roland Thibaudeau, 203 des Erables, Québec.
Secretary: Dr. Euclide Dechêne, 312 du Roi, Québec.
Place: Quebec. Time: May and November.

Societá Italiana di Pediatria

President: Prof. Giuseppe Caronia.
Vice-Presidents: Prof. Mario Cotellessa and Prof. Gaetano Salvioli.
Secretary: Prof. Rolando Bulgarelli.

South African Paediatric Association

Chairman: Dr. H. L. Wallace, Durban.
Honorary Secretary-Treasurer: Dr. F. Walt, 126 Trust Bulidings, Gardiner St., Durban.

Swedish Association of Pediatrics

President: Prof. Sture Siwe, Lund.
Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Docent Justus, Ström, Stockholm.
Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm. Time: Second Friday of each month, except summer.

UNITED STATES

National

American Medical Association, Section on Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia 1. S. C.
Vice-Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Wyman C. C. Cole, 3001 W. Grand Blvd., Detroit 2.

American Academy of Pediatrics

President: Dr. Crawford Bost, 115 Terrace Dr., San Francisco 27.
Vice-President: Dr. Harry Bakwin, 132 E. 71st St., New York 21.
Executive Secretary: Dr. E. H. Christopherson, 610 Church St., Evanston, Ill.
Treasurer: Dr. Edgar E. Martmer, 693 Washington Rd., Grosse Point 30, Mich.

Society for Pediatric Research

President: Dr. Russell Blattner.
Vice-President: Dr. Harold E. Harrison.
Secretary-Treasurer: Dr. Sydney S. Gellis, Boston.

The American Pediatric Society

President: Dr. Alfred H. Washburn, 2257 Ash St., Denver 7.
Vice-President: Dr. Amos U. Christie, Vanderbilt Hospital, Nashville 4, Tenn.
Secretary-Treasurer: Dr. Aims C. McGuinness, 1427 I St., N. W., Washington 5, D. C.

Sectional

Intermountain Pediatric Society

President: Dr. John T. Mason.
Secretary: Dr. Stanley R. Child.
Place: Ambassador Athletic Club, Salt Lake City. Time: 7 p.m.

New England Pediatric Society

President: Dr. Reuben C. Bates, 122 Waterman St., Providence, R. I.
Vice-President (President-Elect): Dr. Louis K. Diamond, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston, except Spring meeting. Time: Wednesdays, four times a year.

North Pacific Pediatric Society

President: Dr. Carl Ashley, 2455 N. W. Marshall St., Portland, Ore.
Secretary-Treasurer: Dr. S. Gorham Babson, 1107 S. W. 13th St., Portland, Ore.

Northwestern Pediatric Society

President: Dr. Stephen D. Mills, Dept. of Pediatrics, Mayo Clinic, Rochester, Minn.
Vice-President: Dr. A. J. Quellette, 1530 Larpenteur Ave., St. Paul, Minn.
Secretary-Treasurer: Dr. T. C. Papermaster, 215 Doctors' Bldg., Minneapolis.
Place: Minneapolis; St. Paul; Duluth, Minn., and Rochester, Minn. Time: January, April, July, and October.

Rocky Mountain Pediatric Society

President: Dr. Edwin Williams.
Vice-President: Dr. Oliver K. Scott.
Secretary-Treasurer: Dr. John H. Githens, Denver.

Southwestern Pediatric Society

President: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Carl A. Erickson, 960 E. Green St., Pasadena, Calif.
Place: Jonathan Club of Los Angeles. Time: 6:30 p.m., second Wednesday in January, March, May, September, and November.

Western Society for Pediatric Research

President: Dr. Robert Aldrich.
Secretary-Treasurer: Dr. Forrest Adams.

State

Alabama Pediatric Society

President: Dr. David B. Monsky, 748 Adams St., Montgomery 5.
Secretary: Dr. Alice H. Pye, 305 Church St., Montgomery.
Place: Montgomery.

Arizona Pediatric Society

President: Dr. Henry E. Running.
Secretary. Dr. William F. Schaffman.
Time: On Call.

California Medical Association, Section on Pediatrics

Chairman: Dr. Joseph W. St. Geme, 511 S. Bonnie Brae, Los Angeles 5.
Secretary: Dr. Alvin H. Jacobs, 2201 Webster St., San Francisco 15.
Assistant Secretary: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills.

Florida State Pediatric Society

President: Dr. Charlotte C. Maguire, 1413 Kuhl Ave., Maguire Bldg., Orlando
Secretary-Treasurer: Dr. Wesley S. Nock, 273 Alhambra Circle, Coral Gables.

Georgia Pediatric Society

President: Dr. John A. Simpson, Athens.
Secretary: Dr. J. Harry Lange, 490 Peachtree St., Atlanta.
Place: Savannah. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Louis Spekter, Division of Crippled Children, Department of Health, State ot Connecticut, Hartford.
Secretary: Dr. Frank E. Roth, 179 Allyn St., Hartford.
Time: With the Connecticut State Medical Society in the spring, with the Connecticut State Clinical Congress in the fall; winter meeting usually in December.

Illinois State Medical Society, Section on Pediatrics

Chairman: Howard R. Miller, 418 Jefferson Bldg., Peoria 2.
Secretary: Harry H. Boyle, 2376 E. 71st St., Chicago 49.

Indiana State Pediatric Society

President: Dr. Harold D. Lynch, Evansville.
Secretary: Dr. L. T. Meiks, Indianapolis.

Iowa Pediatric Society

President: Dr. P. E. Gibson, 1503 Brady St., Davenport.
Vice-President: Dr. Arlan F. Harrington, 924 M. N. B. Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting. Fall meeting in Sept., at University Hospital, Pediatric Dept., Iowa City.

Kansas State Pediatric Society

President: Dr. Bertrand I. Krehbiel, 918 W. 10th St., Topeka.
Secretary: Dr. C. T. Hinshaw, 357 N. Hillside, Wichita.
Time and Place: May, Hutchinson; September, Emporia.

Kentucky Pediatric Society

President: Dr. Alex J. Steigman, University of Louisville School of Medicine, Louisville.
Vice-President: Dr. Daniel B. McIlvoy Jr., Bowling Green.
Secretary-Treasurer: Dr. Selby V. Love, 108 Cannons Lane, Louisville 6.
Place: Louisville. Time: Spring.

Louisiana State Pediatric Society

President: Dr. Jack E. Strange, 3439 Prytania, New Orleans.
Vice-President: Dr. Charles E. Anderson, 1560 Line, Shreveport.
Secretary: Dr. Joseph M. Perret Jr., 2329 S. Carrollton, New Orleans.
Treasurer: Dr. William C. Rivenbark, 1448 Louisiana Ave., New Orleans.
Place: New Orleans. Time: May.

Massachusetts Hospital Association

President: Dr. Philip D. Bonnet, Administrator, Massachusetts Memorial Hospitals, Boston.
Executive Secretary: Henry G. Brickman, 14 Somerset St., Boston 8.

Michigan State Medical Society, Pediatric Section

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary: Dr. Park S. Bradshaw, 1014 Jefferson St., Muskegon.

Montana Pediatric Society

President: Dr. Orville M. Moore, 555 Fuller Ave., Helena.
Secretary: Dr. Joseph W. Brinkley, 410 Central Ave., Great Falls.
Place: Variable. Time: Spring and fall.

Nebraska Pediatric Society

President: Dr. Paul Bandroft, Lincoln.
Vice-President: Dr. Charles Tompkins.
Secretary-Treasurer: Dr. A. J. Lombardo, 401 Aquila Ct., Omaha.
Place: Children's Memorial Hospital. Time: 6 p.m., dinner, third Thursday of each month.

New Hampshire Pediatric Society

President: Dr. MacLean J. Gill, 1 South St., Concord.
Secretary-Treasurer: Dr. Robert F. Wilson, 113 Locust St., Dover.
Place: Alternately Concord, Hanover, Laconia, and Manchester. Time: Four times a year.

New Mexico Pediatric Society

President: Dr. M. K. Wylder, Suite 14, Medical Arts Sq., Albuquerque.
Secretary: Dr. Ly Werner, Suite 25, Medical Arts Sq., Albuquerque.
Place: Variable. Time: Every two or three months.

North Carolina Pediatric Society

President: Dr. Wilburt C. Davison, Duke Hospital, Durham.
President-Elect: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.
Secretary: Dr. William H. Davis Jr., 720 W. 5th St., Winston-Salem.
Time and Place: Roaring Gap, Sept. 17, 1955, and Durham, Nov. 18 and 19, 1955.

South Carolina Pediatric Society

President: Dr. Walter Moore Hart, 117 W. Cheves St., Florence.
Secretary: Dr. John R. Paul Jr., 82 Rutledge Ave., Charleston.
Place: Columbia, S. C. Time: Second Monday and Tuesday in September.

Tennessee Pediatric Society

President: Dr. O. L. Von Canon, 846 McCallie Ave., Chattanooga.
Secretary: Dr. Oliver W. Hill, 4807 Newcom Ave., Knoxville.

Texas Pediatric Society

President: Dr. M. C. Carlisle, Waco.
President-Elect: Dr. Russell Blattner, Houston.
Secretary: Dr. James N. Walker, Fort Worth.
Treasurer: Dr. Jack M. Woodall, Big Springs.

Virginia Pediatric Society

President: Dr. T. J. Humphries, Roanoke.
Vice-President: Dr. F. R. Hopkins, Lynchburg.
Secretary-Treasurer: Dr. A. P. Booker, Charlottesville.

Wisconsin State Medical Society, Section of Pediatrics

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave., Cleveland 12.
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p.m., October, December, February, and March.

Akron Pediatric Society

President: Dr. Joseph M. Ulrich.
Vice-President: Dr. Lewis E. Rector.
Secretary-Treasurer: Dr. Max E. Griffin.
Time: Quarterly.

Baltimore City Medical Society, Pediatric Section

President: Dr. Wilson Grubb, 4 E. 33d St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.
Place: 1211 Cathedral St., Baltimore 1. Time: 8:30 p.m., second Tuesday in November, January, and March.

Bronx Pediatric Society

President: Dr. M. H. Grand, 1749 Grand Concourse, New York.
Secretary: Dr. Charles T. Fried, 1220 Grand Concourse, New York.
Place: Morrisania City Hospital. Time: 8:30 p.m., second Wednesday of each month, except June, July, August, and September.

Brooklyn Academy of Pediatrics

President: Dr. Joseph Battaglia, 713 Bushwick Ave.
Secretary: Dr. A. H. Emerson, 7721 Ridge Blvd.
Place: Granada Hotel, Brooklyn. Time: 8:45 p.m., fourth Wednesday of February, March, April, October, and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold.
Secretary: Dr. Richard A. Downey.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p.m., first Monday of each month, September to June.

Central New York Pediatric Club

President: Dr. Frank Williams, 58 Swan St. S., Albany.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.
Place: Various cities in New York State; fall meeting jointly with Upper New York State Academy of Pediatrics. Time: Third Tuesday of April and October.

Central Ohio Pediatric Society

President: Dr. O. W. Hosterman, 350 East Broad St., Columbus 15.
Secretary-Treasurer: Dr. John Riepenhoff, 2998 Sullivant Ave., Columbus.
Place: As announced. Time: Third Wednesday of September, November, January, March, and May.

Chicago Pediatric Society

President: Dr. Eugene T. McEnery.
Vice-President: Dr. Maxwell P. Borovsky.
Secretary: Dr. Ralph H. Kunstadter, 104 S. Michigan Blvd.
Treasurer: Dr. Noel G. Shaw.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. John E. Allen, 3402 Clifton Ave.
Vice-President: Dr. Robert A. Lyon, Children's Hospital.
Secretary-Treasurer: Dr. William D. De Vaux, 7373 Brookcrest Ave.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. M. Kurzner.
Vice-President: Dr. Jack McKemie.
Secretary-Treasurer: Dr. Hannah B. Woody.
Place: La Louisiane Restaurant. Time: 7.30 p.m., third Wednesday of January, March, May, July, September, and November.

Dade County Pediatric Society

President: Dr. Lynn Whelchel, DuPont Bldg., Miami, Fla.
Secretary: Dr. Howard Engle, 311 Lincoln Rd., Miami Beach, Fla.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.
Place: Children's Hospital of Texas. Time: 6:30 p.m., first Thursday in each month.

Detroit Pediatric Society

President: Dr. Wolf Zuelzer.
Secretary: Dr. Mario S. Cioffari.
Place: Variable. Time: Five times a year.

Fort Worth Pediatric Society

President: Dr. M. W. Brous, 921 Eighth Ave.
Secretary-Treasurer: Dr. William D. Diamond, 554 S. Summit.
Place: Variable: Time: 6 30 p.m., third Friday of each month.

Honolulu Pediatric Society

President: Dr. John Peyton, Medical Group, 1133 Punchbowl St.
Recording Secretary: Goonzo Yamashita, 1618 S. King St.
Corresponding Secretary-Treasurer: Dr. H. M. Sexton, Straub Clinic, 1020 Kapiolani St.
Place: At doctors' homes in rotation. Time: 6 p.m., third Thursday of each month.

Houston Pediatric Society

President Dr. Fred M. Taylor, Baylor University College of Medicine.
Secretary: Dr. William Betts, 4205 Leeland.
Place: River Oaks Country Club. Time 6:30 p.m., fourth Tuesday of alternate months.

Kansas City Southwest Pediatric Society

President: Dr. Frank Houge, Plaza Medical Bldg., Kansas City, Mo.
Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.
Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave., Long Beach, Calif.
Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave., Long Beach, Calif.
Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Robert Shirley, 133 S. Lasky Dr., Beverly Hills, Calif.
Vice-President: Dr. Deron Housepian, 960 E. Green St., Pasadena, Calif.
Secretary: Dr. Margaret Jones, 405 Hilgard Ave., University of California School of Medicine at Los Angeles, Los Angeles 24.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd., Los Angeles. Time: Second Thursday of alternate months beginning in September.

Louisville Pediatric Society

President: Dr. Harry S. Andrews.
Vice-President: Dr. Joseph Little.
Secretary-Treasurer: Dr. Kenneth P. Crawford.
Place: Variable. Time: Five times a year, as announced.

Medical Society of the County of Kings and Academy of Medicine of Brooklyn, Pediatric Section

President: Bernard Greenberg, 755 Ocean Ave., Brooklyn 26.
Vice-President: Dr. Joseph Pincus, 881 Washington Ave., Brooklyn 25.
Secretary: Dr. Arthur L. Ruby, 1331 E. 19th St., Brooklyn 30.
Treasurer: Dr. David Dragutsky, 179 Marlboro Rd., Brooklyn.
Place: Kings County Medical Society Auditorium, 1313 Bedford Ave., Brooklyn. Time: 8:45 p.m., fourth Monday of January, March, April, October, and November.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington 20.
Secretary: Dr. John E. Cassidy, 5402 Connecticut Ave. N.W., Washington.
Place: Medical Society Bldg., 1718 M St. N.W., Washington. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. Clifton W. Woolley, 2448 Poplar Ave.
Vice-President: Dr. Steve H. Turnbull, 848 Adams.
Secretary-Treasurer: Dr. Charles H. Householder, 321 S. Bellevue.
Place: Rotated among four hospitals. Time: 7:30 p.m., second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. Kenneth Winters, Wauwatosa, Wis.
Secretary: Dr. James P. Conway, Milwaukee.
Place: Milwaukee University Club. Time: Second Wednesday of February, April, June, and October.

Mobile Pediatric Society

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.
Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile, Ala.
Place: Admiral Semmes Hotel. Time: 7:30 p.m., fourth Thursday of September, November, January, March, and May.

Nashville Pediatric Society

President: Dr. Thomas Weaver, Bennie Dillon Bldg., Nashville, Tenn.
Secretary: Dr. Ethel Walker, 3415 West End Ave., Nashville, Tenn.
Place: Homes of members. Time: Third Thursday of every month.

Nassau Pediatric Society

President: Dr. John J. Eppig, 3096 Northern Blvd., Manhasset, N. Y.
Vice-President: Dr. Ralph M. Burns, Professional Center, Glen Head, N. Y.
Secretary-Treasurer: Dr. David J. Posner, 98 Walcott Rd., Levittown, N. Y.
Place: Felice's Restaurant, Post Ave., Westbury, N. Y. Time: 9:00 p.m., second Monday of October, December, February, April, and June.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Jerome L. Kohn, 50 W. 96th St., New York 25.
Secretary: Dr. Lawrence B. Slobody, 1 E. 105th St., New York 12.
Place: New York Academy of Medicine, 2 E. 103d St. Time: 8:30 p.m., second Thursday of each month, November to May, inclusive.

Northern California Pediatric Society

President: Dr. Edward Campion, 707 C St., San Rafael.
Secretary-Treasurer: Dr. Joseph H. Davis, 300 Homer Ave., Palo Alto.
Place: San Francisco. Time: Quarterly, as speakers are available.

Northern Ohio Pediatric Society

President: Dr. Earl E. Smith.
President-Elect: Dr. Chauncey Wyckoff.
Secretary-Treasurer: Dr. C. Q. McClelland.

Oklahoma City Pediatric Society

President: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Louis Frank, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. Norman Kendall, 3401 N. Broad St., Philadelphia 40.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p.m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. W. W. Briant, 633 Washington Rd.
Vice-President: Dr. Robert R. Macdonald, 448 Brownsville Rd.
Secretary-Treasurer: Dr. Bernard I. Michaels, 3500 Fifth Ave.
Place: Western State Psychiatric Institute and Clinic. Time: October, December, February, and April.

Queens Pediatric Society

President: Dr. Moe Goldstein, 111-32 76th Ave., Forest Hills, N. Y.
Secretary: Dr. John Finnegan, 36-19 Bowne St., Flushing, N. Y.
Place: Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.
Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p.m., third Thursday of each month, except June, July, and August.

San Antonio Pediatric Society

President: Dr. Philip Magrish, 402 Fulton Ave.
Secretary: Dr. Jack M. Wright, 403 Summit Ave.
Time: 7:30 p.m., supper, first Tuesday of each month.

St. Louis Pediatric Society

President: Dr. H. E. Wachter, 8505 Delmar.
Vice-President: Dr. Raymond J. LaDriere, 35 No. Central, Clayton 5, Mo.
Secretary-Treasurer: Dr. Leo F. Gowen, 337 W. Lockwood, Webster Groves 19, Mo.
Place: Medart's Restaurant. Time: 7 p.m., second Thursday of each month from September to May, inclusive.

Santa Barbara Pediatric Society

President: Dr. Clarence B. Hills, 22B. W. Micheltorena St., Santa Barbara, Calif.
Secretary: Dr. Louise P. Brown, 3017 Foothill Rd., Santa Barbara, Calif.
Place: Varies. Time: Two to three times yearly, on call.

Seattle Pediatric Society

President: Dr. O. William Anderson.
President-Elect: Dr. Robert Tidwell.
Secretary-Treasurer: Dr. James L. Tucker.
Place: College Club. Time: 6:30 p.m., fourth Friday of each month from September to June.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Fred J. Chapin, 101 John St., Bay City.
Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Ann Arbor.
Place: University Hospital, Ann Arbor.

Waco Pediatric Society

President: Dr. F. W. Hoehn.
Secretary: Dr. M. C. Carlisle.
Place: 1918 Austin Ave., Waco, Texas. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

Chairman: Dr. Donald R. Reed, 14 S. Broadway, Irvington, N. Y.
Secretary: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Four dinner meetings a year, November, February, April, and June.

Western Michigan Pediatric Society

President: Dr. A. Morgan Hill, 310 Fulton, E., Grand Rapids.
Secretary: Dr. John C. Montgomery, 1810 Wealthy St., S.E., Grand Rapids.
Place: Two meetings in Grand Rapids, two elsewhere. Time: First Wednesday of October. November, April, and May.

Wichita Pediatric Society

President: Dr. Mary Blood.
Secretary: Dr. R. A. Nelson.
Place: Homes of members. Time: 8:30 p.m., first Thursday, October through May.

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- Rapidly attained therapeutic levels
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A palatable, spice-flavored antihistamine, Pyribenzamine Elixir offers highly effective therapy in a broad range of allergies. *Dosage can be readily adjusted* to any age, any individual requirement. *Prescribe this well-accepted medication* alone or as a therapeutic vehicle. Each 4-ml. teaspoonful contains 30 mg. Pyribenzamine citrate.

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Meat...

and the Prevention and Treatment of Nutritional Edema in Children

Nutritional edema, a state of protein deficiency resulting from inadequate protein consumption, occurs sporadically and has been endemic in areas of the South.[1] A high incidence of hypoproteinemia just above edema levels has been reported in clinic children in a large Southern city.[2] Diets deficient in protein are usually inadequate in other essentials; nutritional hypoproteinemia in many instances may be accompanied by deficiencies in B vitamins and in iron.

To prevent nutritional edema in children, an adequate protein intake must be maintained. To cure the uncomplicated case, the only treatment needed is a high caloric, high protein diet supplying largely protein from animal sources. When the protein in the diet is of this high biologic value, the total quantity of protein required is less than when it is derived chiefly from vegetable sources.[1]

Because of its high content of anabolically effective protein containing all the essential and many other amino acids, meat contributes valuably to the protein adequacy of diets. In addition, generous amounts of meat supply high proportions of the daily allowances of B vitamins and essential minerals—especially iron, phosphorus, and potassium—needed for good nutrition.

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1. Nelson, W. E.: Nutritional Edema (Protein Deficiency, Hypoproteinemia, War Edema), in Nelson, W. E.: Textbook of Pediatrics, ed. 6, Philadelphia, W. B. Saunders Company, 1954, pp. 308-309.

2. Dodd, K., and Minot, A. S.: Edema in Infancy and Childhood as Expression of Chronic Dietary Insufficiency, J. Pediat. *8*:442 (Apr.) 1936; Occurrence of Moderately Reduced Serum Albumin in 500 Children in a Southern Clinic, ibid *8*:452 (Apr.) 1936.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago... Members Throughout the United States

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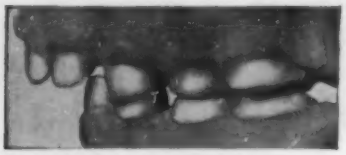

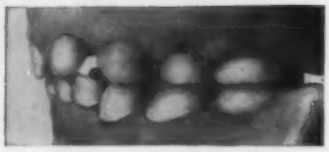

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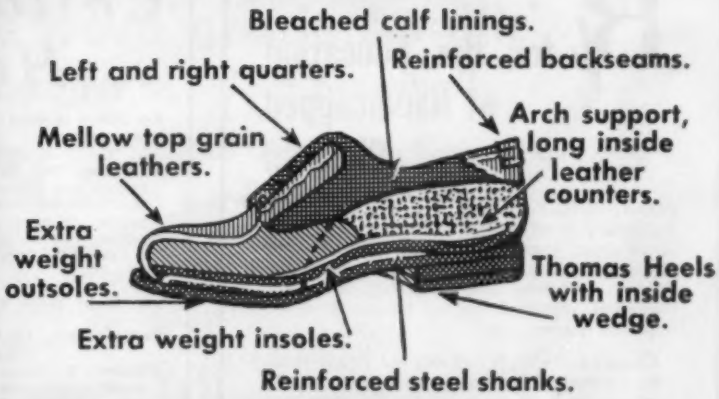

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(1) Jeans, P. C., in A. M. A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, pp. 275-278.

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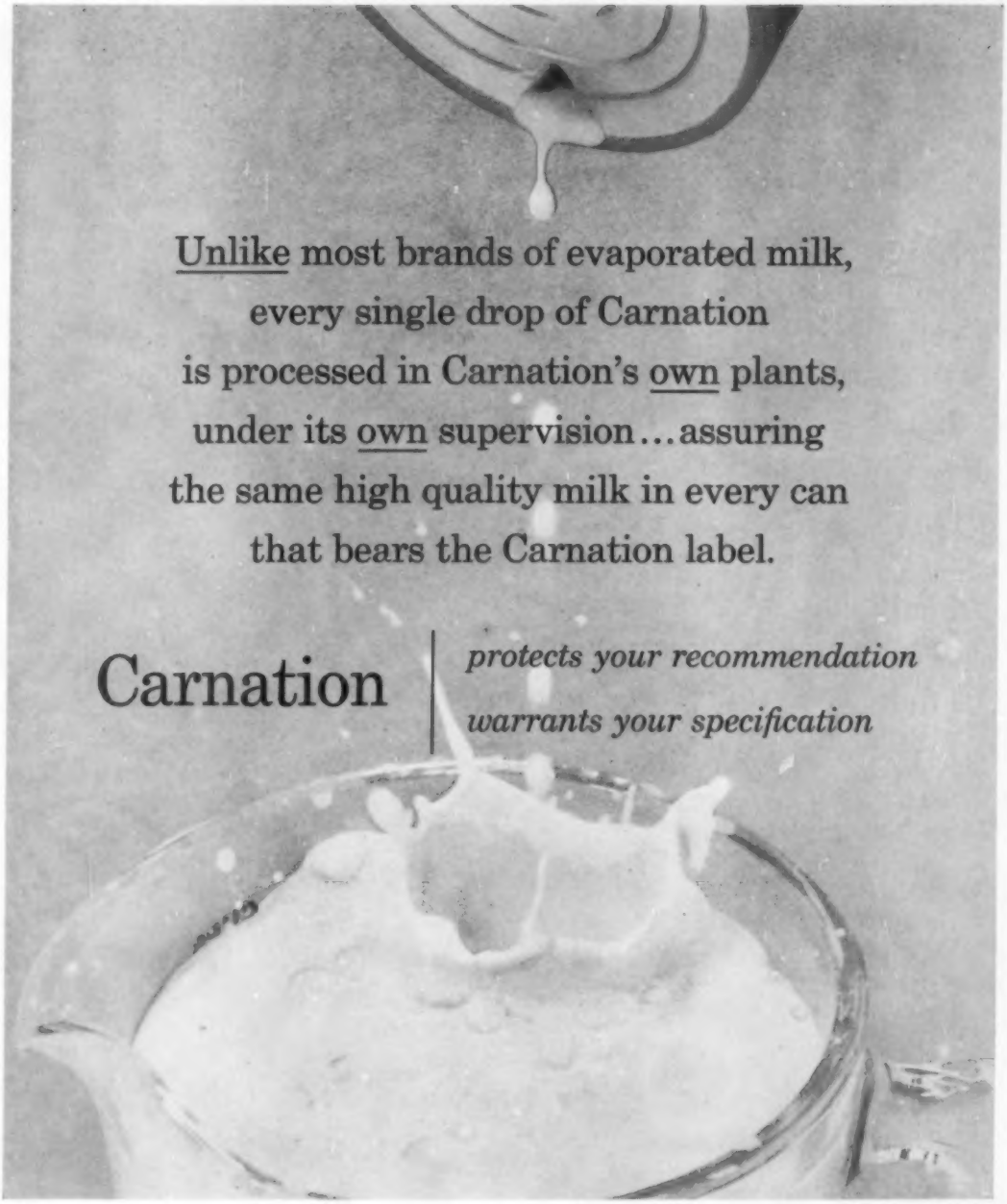
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